Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: RICHARD SCHNIZER Examiner #: 76557 Date: 12/30/02
Art Unit: 1635 Phone Number 306-5941 Serial Number: 09/855,176
Mail Box and Bldg/Room Location: CM1 11E12 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.
****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc. if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

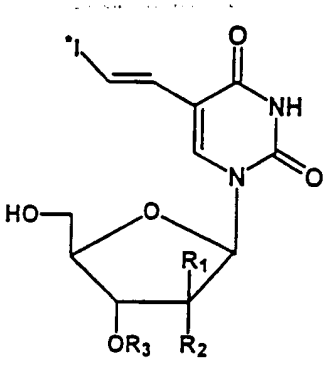
Title of Invention: COMBINED USE OF NUCLEOSIDE ANALOGUES AND GENE TRANSFECTION

Inventors (please provide full names): EDWARD E. KNAUS, LEONARD I. WIEBE, KEVIN MORIN

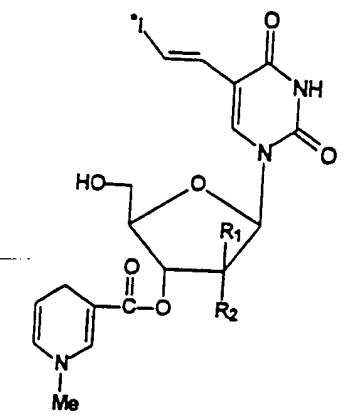
Earliest Priority Filing Date: ~~09/~~ 7/14/97

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

PLEASE SEARCH THE FOLLOWING STRUCTURES



IVFAU (R_1 = F, R_2 = H, R_3 = H)
IVAU (R_1 = OH, R_2 = H, R_3 = H)
IVDU (R_1 = H, R_2 = H, R_3 = H)
[*I] = 123I, 124I, 125I, 131I, Any Halogen



[*I]-IVFAU-CDS (R_1 = F, R_2 = H)
[*I]-IVAU-CDS (R_1 = OH, R_2 = H)
[*I]-IVDU-CDS (R_1 = H, R_2 = H)
[*I] = 123I, 124I, 125I, 131I, Any Halogen

Point of Contact:
Thomas G. Larson, Ph.D.
703-308-7309
CM1, Rm. 6 B 01

Can Rush

****

STAFF USE ONLY

Searcher: Point of Contact: Thomas G. Larson, Ph.D.
Searcher Phone #: ~~703-308-7309~~
Searcher Location: CM1, Rm. 6 B 01
Date Searcher Picked Up: 12/30/02
Date Completed: 01/02/03
Searcher Prep & Review Time: 60
Clerical Prep Time: _____
Online Time: 107

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) 2
Bibliographic _____
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN #569
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

PTO-1590 (8-01)

First Compound listed on Search Request


```
=> file reg hcaplus
FILE 'REGISTRY' ENTERED AT 13:27:43 ON 02 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 American Chemical Society (ACS)

FILE 'HCAPLUS' ENTERED AT 13:27:43 ON 02 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

=> d que l43
L18             STR
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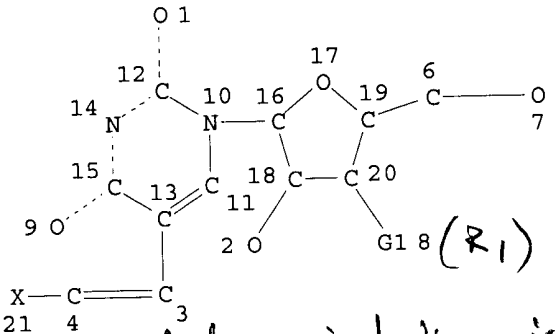
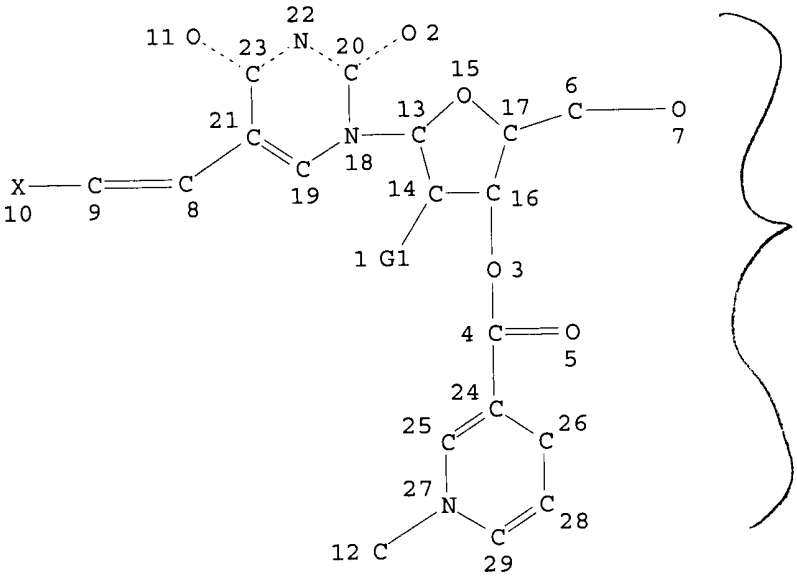


X = any halogen including isotopes of I.

R1: VAR G1=H/OH/F
NODE ATTRIBUTES:
CONNECT IS E1 RC AT 2 Exactly 1 non-H connection allowed @ 2-limits
CONNECT IS E1 RC AT 7
CONNECT IS X3 RC AT 20 R_3 to H
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L19 STR



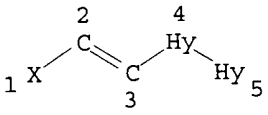
second structure listed on search request — used to remove duplicate answers.

Point of Contact:
Thomas G. Larson, Ph.D.
703-308-7309
CM1, Rm. 6 B 01

VAR G1=H/OH/F
NODE ATTRIBUTES:
CONNECT IS E1 RC AT 7
CONNECT IS E3 RC AT 16
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 29

STEREO ATTRIBUTES: NONE
L20 STR



initial structure Hy @ 4 limited to 4C 2N and Hy @ 5 limited to 4C 1O.

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY UNS AT 4
GGCAT IS MCY SAT AT 5
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E4 C E2 N AT 4
ECOUNT IS E4 C E1 O AT 5

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 5

STEREO ATTRIBUTES: NONE
L22 715 SEA FILE=REGISTRY SSS FUL L20 - initial answer set using structure L20 to search.
L24 33 SEA FILE=REGISTRY SUB=L22 SSS FUL L18 - Search answer set L22 with structure L18
L26 19 SEA FILE=REGISTRY SUB=L22 SSS FUL L19
L28 6 SEA FILE=CAPLUS ABB=ON PLU=ON L26 } - Results from search for second requested structure
L30 53165 SEA FILE=HCAPLUS ABB=ON PLU=ON TRANSFORMATION, GENETIC+NT,PFT

Searched by Thom Larson, STIC, 308-7309

controled terms relating to transfection

Initial answer set in HCAPLUS was 261 hits. Narrow by using search terms related to utility of compounds

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L31        2886 SEA FILE=HCAPLUS ABB=ON  PLU=ON  TRANSDUCTION, GENETIC+NT,PFT/C
                T
L32        5674 SEA FILE=HCAPLUS ABB=ON  PLU=ON  TRANSGENE+NT,PFT/CT
L33       59541 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L30 OR L31 OR L32
L35      114239 SEA FILE=HCAPLUS ABB=ON  PLU=ON  VIRUS, ANIMAL+NT,PFT/CT
L41         135 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 (L) (PREP OR THU OR
                BAC)/RL
L42          39 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L41 AND (L35 OR L31 OR L32 OR
                L33)
L43          37 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L42 NOT L28
```

Remove answers duplicated in search for 2nd compound

I've saved the initial answer set - if you would like to narrow it another way - let me know.

=> D IBIB ABS HITSTR 143 1-37

L43 ANSWER 1 OF 37 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:935354 HCAPLUS
DOCUMENT NUMBER: 136:64094
TITLE: The use of synthetic, non-hormonal 21-aminosteroids, derivatives, metabolites, and precursors thereof in the treatment of viral infections
INVENTOR(S): Prendergast, Patrick Thomas
PATENT ASSIGNEE(S): Kotze, Gavin Salomon, S. Afr.
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001097749	A2	20011227	WO 2001-IB1101	20010622
WO 2001097749	A3	20020523		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2001074383	A5	20020102	AU 2001-74383	20010622

PRIORITY APPLN. INFO.:

IE 2000-511	A	20000623
IE 2001-275	A	20010321
WO 2001-IB1101	W	20010622

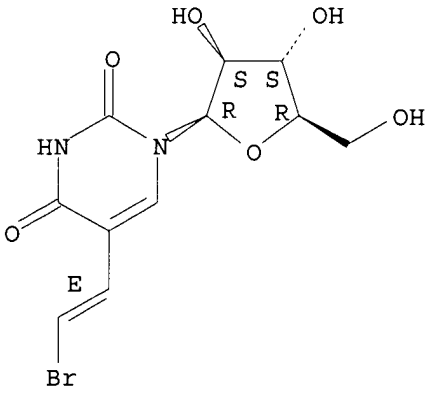
AB The invention discloses the use of synthetic, non-hormonal 21-aminosteroids, derivs., metabolites, and precursors thereof in the treatment of viral infections, particularly hepatitis and retroviral infection by HIV. Synthetic non-hormonal 21-aminosteroids are disclosed for use in the prophylaxis and therapy of hepatitis viral infections. These compds. can be administered alone or in combination with conventional antiviral agents.

IT **77181-69-2**, Sorivudine
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(aminosteroids, derivs., metabolites, and precursors for treatment of viral infection, and use with other agents)

RN 77181-69-2 HCAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 2 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:652187 HCAPLUS
DOCUMENT NUMBER: 127:341435
TITLE: Varicella-zoster virus thymidine kinase gene and antiherpetic pyrimidine nucleoside analogs in a combined gene/chemotherapy treatment for cancer
AUTHOR(S): Degreve, B.; Andrei, G.; Izquierdo, M.; Piette, J.; Morin, K.; Knaus, E. E.; Wiebe, L. I.; Basrah, I.; Walker, R. T.; De Clercq, E.; Balzarini, J.
CORPORATE SOURCE: Lab. Virol. Chemother., Rega Inst. Med. Res., Kathol. Univ. Leuven, Belg.
SOURCE: Gene Therapy (1997), 4(10), 1107-1114
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ten pyrimidine nucleoside analogs, including (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) and closely related analogs, were evaluated for their cytostatic activity against human osteosarcoma cells transfected with the varicella-zoster virus (VZV) thymidine kinase (tk) (ATP:thymidine 5' phosphotransferase, EC 2.7.1.21) gene. (E)-5-(2-bromovinyl)-1-.beta.-D-arabinofuranosyluracil (BVaraU), (E)-5-(2-iodovinyl)-2'-deoxy-2'-fluoro-1-.beta.-D-arabinofuranosyluracil (IVFAU) and (E)-5-(2-bromovinyl)-2'-deoxy-4'-thiouridine (S-BVDU) were among the most potent inhibitors of VZVtk gene-transfected cell proliferation. They displayed an inhibitory activity at drug concns. that were up to four orders of magnitude lower than those required to inhibit the corresponding nontransfected tumor cells. Inhibition of cellular DNA polymerase and/or incorporation of the drugs into cellular DNA may be a likely target for the cytostatic activity of the BVDU derivs. against the VZVtk gene-transfected tumor cells. These compds. were approx. 40- to 80-fold more potent cytostatic agents in VZVtk gene-transfected cells than the anti-VZV compd. 6-methoxy-9-.beta.-D-arabinofuranosylpurine (araM), and at least five- to 50-fold more cytostatic than ganciclovir in HSV-1tk gene-transfected murine mammary carcinoma FM3A cells. In addn., the intrinsic resistance of BVaraU, IVFAU and S-BVDU to glycosidic bond cleavage by mammalian dThd phosphorylases makes them promising candidate compds. for the treatment of VZVtk

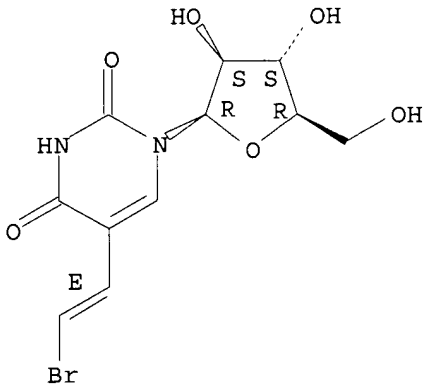
gene-transfected tumors in vivo.

IT **77181-69-2**, BVaraU
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(varicella-zoster virus thymidine kinase gene and antiherpetic pyrimidine nucleoside analogs in a combined gene/chemotherapy treatment for cancer)

RN 77181-69-2 HCAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 3 OF 37 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:594451 HCAPLUS

DOCUMENT NUMBER: 125:292318

TITLE: Phenotypic resistance of herpes simplex virus type 1 strains selected in vitro with antiviral compounds and combinations thereof

AUTHOR(S): Morfin, F.; Snoeck, R.; Andrei, G.; De Clercq, E.

CORPORATE SOURCE: Rega Inst. Med. Res., Katholieke Universiteit Leuven, Louvain, B-3000, Belg.

SOURCE: Antiviral Chemistry & Chemotherapy (1996), 7(5), 270-275
CODEN: ACCHEH; ISSN: 0956-3202

PUBLISHER: Blackwell

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Several drug resistant herpes simplex virus type 1 (HSV-1) strains were obtained under the selective pressure of various antiherpetic drugs used alone or in combination. Their susceptibility to a wide range of antiviral compds. was detd. Strains selected under the pressure of brivudine (BVDU) or 1-.beta.-D-arabino-furanosyl-(E)-5-(2-bromovinyl)uracil (BVaraU) alone were composed of two virus populations: (1) virus resistant to BVDU and BVaraU bot not to acyclovir (ACV) or ganciclovir (GCV), which is suggestive of an alteration in the thymidylate kinase activity assocd. with viral thymidine kinase (TK) (responsible for the phosphorylation of BVDU-monophosphate to BVDU-diphosphate); and (2) virus resistant to TK-dependent drugs (i.e. ACV, GCV, BVDU and BVaraU) as well as double-mutant strains with decreased sensitivity to both TK-dependent compds. and the pyrophosphate analogs foscarnet (PFA) and

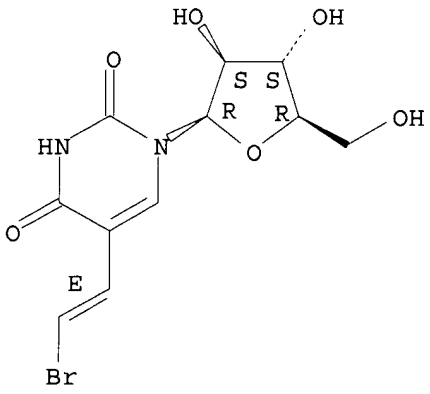
phosphonoacetic acid (PAA) (suggestive of mutations at the level of the DNA polymerase) were recovered under the selective pressure of ACV alone or in combination with BVDU or BVaraU. Combinations of BVDU or BVaraU with PFA or PAA led to strains resistant only to BVDU and BVaraU or double-mutant strains resistant to BVDU, BVaraU and the pyrophosphate analogs, but not to strains resistant to other TK-dependent drugs. Interestingly, strains resistant to ACV, BVDU, GCV and/or the pyrophosphate analogs PFA and PAA remained sensitive to the (S)-3-hydroxy-2-phosphonyl-methoxypropyl (HPMP) derivs. of cytosine (HPMPC) and adenine (HPMPA).

IT **77181-69-2**, BVaraU
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(phenotypic resistance of herpes simplex virus type 1 strains selected in vitro with antiviral compds. and combinations thereof)

RN 77181-69-2 HCAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 4 OF 37 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1996:593957 HCAPLUS
DOCUMENT NUMBER:	125:230830
TITLE:	Topical preparations containing virucides and anti-inflammatory glucocorticoids for treatment of herpes virus infections
INVENTOR(S):	Harmenberg, Johan Georg; Kristofferson, Ann Harriet Marg
PATENT ASSIGNEE(S):	Astra Aktiebolag, Swed.
SOURCE:	PCT Int. Appl., 31 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9624355	A1	19960815	WO 1996-SE124	19960202

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE,

ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE

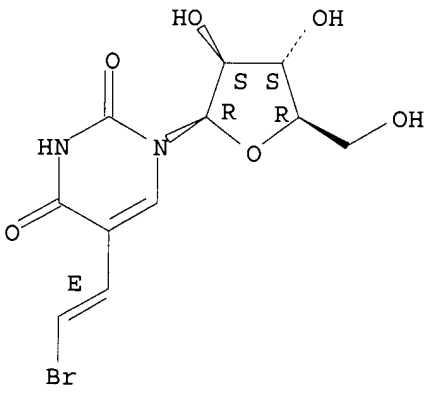
TW 438585	B	20010607	TW 1996-85100236	19960110	
ZA 9600527	A	19960806	ZA 1996-527	19960123	
CA 2211389	AA	19960815	CA 1996-2211389	19960202	
AU 9646821	A1	19960827	AU 1996-46821	19960202	
AU 716809	B2	20000309			
EP 809498	A1	19971203	EP 1996-902557	19960202	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV					
JP 11506417	T2	19990608	JP 1996-524189	19960202	
US 6337324	B1	20020108	US 1996-612847	19960308	
NO 9703612	A	19970926	NO 1997-3612	19970805	
FI 9703243	A	19970806	FI 1997-3243	19970806	
PRIORITY APPLN. INFO.:			WO 1995-SE114	A 19950206	
			WO 1996-SE124	W 19960202	

AB The invention relates to pharmaceutical compns. for topical administration comprising a topically acceptable antiviral substance and an anti-inflammatory glucocorticoid in a pharmaceutically acceptable carrier. The pharmaceutical compn. can be used in the prophylactic and curative treatment of herpes virus infections in mammals including man. For example, a cream contained budesonide 0.125, trisodium phosphonoformate hexahydrate 15, Na citrate 0.6, citric acid 0.3, sorbic acid 0.3, cetostearyl alc. 30, paraffin liq. 3, cetomacrogol 1000 6, white soft paraffin 15, Arlatone 31, cetyl alc. 14, stearic acid 14, mineral oil 14, propylene glycol 14, glycerol 10.5, methylparaben 0.43, propylparaben 0.19 and water to 10000 mg.

IT **77181-69-2**, Sorivudine
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(topical compns. contg. virucides and anti-inflammatory glucocorticoids for treatment of herpes virus infections)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 5 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:502144 HCAPLUS

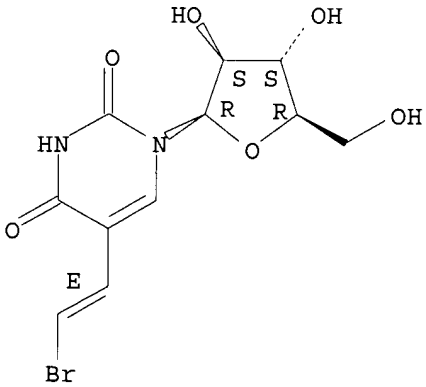
DOCUMENT NUMBER: 125:131823
TITLE: Treatment of adult varicella with sorivudine: A randomized, placebo-controlled trial
AUTHOR(S): Wallace, Mark R.; Chamberlin, Carolyn J.; Sawyer, Mark H.; Arvin, Ann M.; Harkins, John; LaRocco, Anthony; Colopy, Mike W.; Bowler, William A.; Oldfield, Edward C. III
CORPORATE SOURCE: Naval Medical Center, University California, San Diego, CA, 92134-5000, USA
SOURCE: Journal of Infectious Diseases (1996), 174(2), 249-255
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antiviral and clin. efficacy of sorivudine in adults with varicella was evaluated in a double-blind, placebo-controlled randomized trial. A total of 186 patients were hospitalized for isolation and treatment within 96 h of rash onset. The diagnosis of varicella was confirmed in 184 patients with paired sera. Patients were randomly assigned to receive 10 or 40 mg of sorivudine or an identical placebo once a day for 5 days. Treatment with 40 mg of sorivudine (compared with placebo) shortened the mean time to 100% crusting from 6.6 to 5.8 days (P = .004) and reduced the mean days that new lesion formed from 3.9 to 3.1 (P = .014). Mean days of cutaneous viral shedding were reduced from 3.3 in the placebo group to 2.6 in the 40-mg sorivudine group (P = .002). The effectiveness of therapy was not affected by the duration of rash before initiation of therapy. Sorivudine is a promising new agent for the treatment of varicella-zoster virus infections.

IT **77181-69-2**, Sorivudine
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(treatment of adult varicella with sorivudine in humans)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 6 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:458107 HCAPLUS
DOCUMENT NUMBER: 125:132726

TITLE: Gene therapy by activation of combinations of pyrimidine nucleoside and nucleobase analogs with fusion proteins of activating enzymes
INVENTOR(S): Tiraby, Gerard; Reynes, Jean-Paul; Tiraby, Michele; Cazaux, Christophe; Drocourt, Daniel
PATENT ASSIGNEE(S): Cayla, Fr.
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

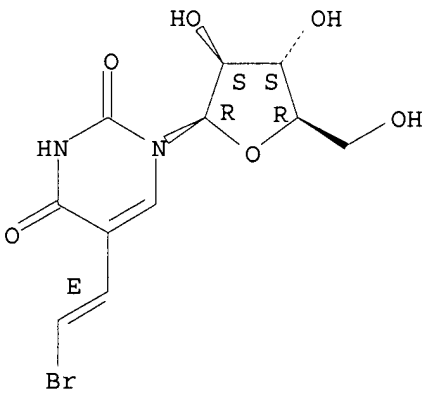
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9616183	A1	19960530	WO 1995-FR1511	19951116
W: AU, CA, JP, KR				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5856153	A	19990105	US 1994-343923	19941117
AU 9641809	A1	19960617	AU 1996-41809	19951116
EP 792369	A1	19970903	EP 1995-940324	19951116
EP 792369	B1	20000405		
R: BE, CH, DE, ES, FR, GB, IT, LI, NL				
ES 2146788	T3	20000816	ES 1995-940324	19951116

PRIORITY APPLN. INFO.: US 1994-343923 A 19941117
WO 1995-FR1511 W 19951116

AB Chimeric genes encoding fusion proteins of enzymes that specifically activate the pyrimidine analogs 5-fluorocytosine and azidothymidine into derivs. toxic for mammalian cells are described. These genes (suicide genes) can be used singly or in combination to kill transfected tumor cells or immune cells with cell-specificity achieved by placing the genes under control of a promoter that is only active in the infected or tumor cell. Furthermore, eukaryotic vectors including two suicide gene expression units, i.e. a first unit sensitizing the tumor cells to 5-fluorocytosine or 5-fluorouracil, and a second making HIV-infected cells synergistically resistant to azidothymidine. The construction of a no. of chimeric genes for fusion proteins and their use in the killing of melanoma cells in vitro is demonstrated. The cells became very sensitive to AZT and fluorocytosine.

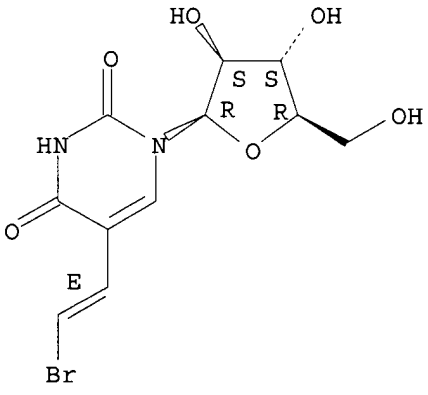
IT **77181-69-2**, Brovavir
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(activation in situ of; gene therapy by activation of combinations of pyrimidine nucleoside and nucleobase analogs with fusion proteins of activating enzymes)
RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 7 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:419256 HCAPLUS
DOCUMENT NUMBER: 125:75082
TITLE: Sorivudine: a potent inhibitor of varicella zoster virus replication
AUTHOR(S): Whitley, Richard J.
CORPORATE SOURCE: University Alabama, Birmingham, AL, USA
SOURCE: Advances in Experimental Medicine and Biology (1996), 394(Antiviral Chemotherapy 4), 41-44
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Plenum
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 11 refs.
IT **77181-69-2**, Sorivudine
RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(varicella zoster virus replication inhibition by)
RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 8 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:181855 HCAPLUS
DOCUMENT NUMBER: 124:250904
TITLE: Compositions of N-(phosphonoacetyl)-L-aspartic acid (PALA)and methods of their use as broad spectrum antivirals
INVENTOR(S): Blough, Herbert A.
PATENT ASSIGNEE(S): U.S. Bioscience, Inc., USA
SOURCE: U.S., 39 pp., Cont.-in-part of U.S. Ser. No. 853,454,abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5491135	A	19960213	US 1993-32234	19930317
ZA 9301934	A	19930318	ZA 1993-1934	19930107
IL 105090	A1	19980816	IL 1993-105090	19930317
CA 2109435	AA	19930919	CA 1993-2109435	19930318
CA 2109435	C	19970311		
WO 9318763	A1	19930930	WO 1993-US2432	19930318
W: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
AU 9339659	A1	19931021	AU 1993-39659	19930318
CN 1080853	A	19940119	CN 1993-104593	19930318
EP 660710	A1	19950705	EP 1993-909132	19930318
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07507770	T2	19950831	JP 1993-516700	19930318
BR 9306123	A	19970826	BR 1993-6123	19930318

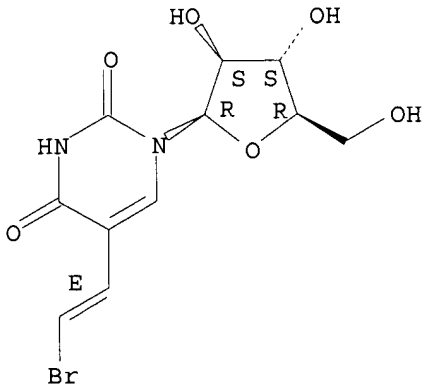
PRIORITY APPLN. INFO.: US 1992-853454 19920318
US 1993-32234 19930317
WO 1993-US2432 19930318

AB Compns. and methods are disclosed which utilize the broad spectrum antiviral activity of PALA. This compd. and its pharmaceutically acceptable analogs possess potent activity while displaying minimal toxicity and, therefore, are characterized by a relatively high therapeutic index. Compns. optionally contg. other therapeutic agents, such as other antiviral agents, are also disclosed and are found to possess synergistic and/or additive antiviral activity.

IT **77181-69-2**, BV-AraU
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(phosphonoacetyl aspartic acid, alone or in combination with other agents, for broad spectrum antiviral, and pharmaceutical compns.)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 9 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:988703 HCAPLUS
DOCUMENT NUMBER: 124:105675
TITLE: Antiviral activity of selected acyclic nucleoside analogs against human herpes virus 6
AUTHOR(S): Reymen, D.; Naesens, L.; Balzarini, J.; Holy, A.; Dvorakova, H.; De Clercq, E.
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, Louvain, B-3000, Belg.
SOURCE: Antiviral Research (1995), 28(4), 343-57
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

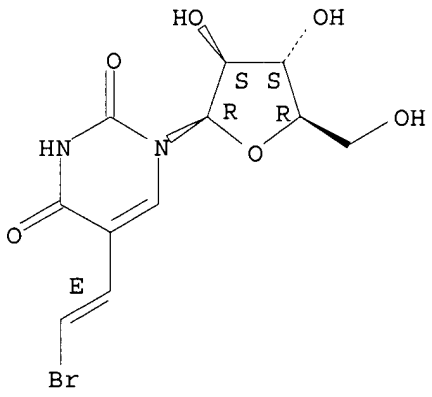
AB Human herpes virus 6 (HHV-6) was examd. in vitro for its sensitivity to a broad range of nucleoside analogs, including acyclovir (ACV), ganciclovir (GCV), penciclovir (PCV), buciclovir (BCV), brivudin (BVDU), the N7-isomer of 6-deoxyganciclovir (S2242), foscarnet (phosphonoformic acid, PFA), and several acyclic nucleoside phosphonate (ANP) analogs such as (S)-HPMPA, (S)-HPMPC, PMEA and PMEDAP. Antiviral efficacy was monitored microscopically by the inhibitory effect of the compds. on HHV-6-induced cytopathic effect in human T-lymphoblastoid HSB-2 cells. In addn., a newly developed immunofluorescence/flow cytometric assay (FACS) was used to det. HHV-6-specific antigen expression. A close correlation was obsd. between the antiviral data obtained by the microscopic assay and the flow cytometric assay. Marked antiviral efficacy was noted for S2242, PFA and the ANP analogs (S)-HPMPA, (S)-HPMPC, (S)-cHPMPC, (S)-3-deaza-HPMPA, (S)-3-deaza-cHPMPA, (S)-HPMPG and (R)-HPMPG. Also, PMEA and PMEDAP proved highly active against HHV-6 infection, whereas (S)-FPMPA and (R)-PMPDAP were inactive. ACV was only slightly protective against HHV-6, and no activity was found for GCV, PCV, BCV and BVDU. Overall, the efficacy of the nucleoside analogs against HHV-6 appeared to correlate with their efficacy against human cytomegalovirus (HCMV).

IT **77181-69-2**, BVaraU
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antiviral activity of selected acyclic nucleoside analogs against human herpes virus 6)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-

bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 10 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:777817 HCAPLUS
DOCUMENT NUMBER: 123:160821
TITLE: Human herpesvirus-6-associated multiple sclerosis: treatments, prevention and diagnosis thereof
INVENTOR(S): Burmer, Glenna C.; Challoner, Peter B.; Smith, Kirsten T.; Brown, Joseph P.; Parker, Jay D.; Nowinski, Robert C.
PATENT ASSIGNEE(S): Pathogenesis Corp., USA
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9512313	A1	19950511	WO 1994-US12655	19941104
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2175806	AA	19950511	CA 1994-2175806	19941104
AU 9510878	A1	19950523	AU 1995-10878	19941104
EP 726708	A1	19960821	EP 1995-901761	19941104
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

PRIORITY APPLN. INFO.:
US 1993-149176 19931105
US 1994-218029 19940324
US 1994-287942 19940805
US 1994-334482 19941104
WO 1994-US12655 19941104

AB Methods are provided for preventing and treating human herpesvirus-6 (HHV-6)-assocd. multiple sclerosis (MS). Also provided are the herpesvirus assocd. with MS, methods for detecting the virus, diagnosing

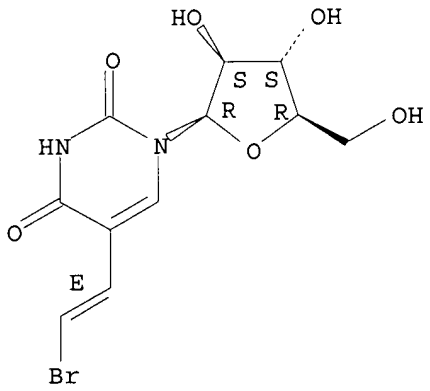
viral-assocd. MS, and methods for screening for herpesvirus-assocd. MS. Identification of HHV-6 nucleic acid sequences in MS is described, as is complete sequencing of MSV-1206 viral genes for phosphotransferase, DNA polymerase, and DNA binding protein.

IT **77181-69-2**, Brovavir
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(diagnosis and treatment human herpesvirus-6-assocd. multiple sclerosis, and characterization and DNA sequences of virus MSV-1206)

RN 77181-69-2 HCAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 11 OF 37 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:740460 HCAPLUS
DOCUMENT NUMBER: 123:160174
TITLE: Comparison of the selectivity of anti-varicella-zoster virus nucleoside analogs
AUTHOR(S): Machida, Haruhiko; Nishitani, Makiko; Watanabe, Yohko; Yoshimura, Yuichi; Kano, Fumitaka; Sakata, Shinji
CORPORATE SOURCE: Biol. Chem. Lab., Yamasa Corp., Chiba, 288, Japan
SOURCE: Microbiology and Immunology (1995), 39(3), 201-6
CODEN: MIIMDV; ISSN: 0385-5600
PUBLISHER: Center for Academic Publications Japan
DOCUMENT TYPE: Journal
LANGUAGE: English

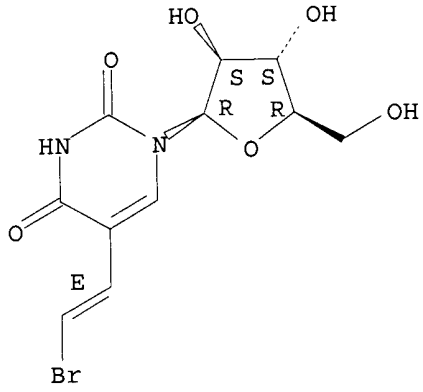
AB The authors compared the selectivity of six anti-varicella-zoster virus (VZV) drugs, which are clin. available or for which clin. efficacy against VZV infections has been reported. Sorivudine (BV-araU) had the most potent anti-VZV effect in the plaque inhibition assay, followed by brivudine (BVDU) and 5-propynyl-arabinofuranosyluracil (Pry-araU). All test compds., except vidarabine (AraA), had only a very weak effect on human embryonic lung cell growth. The selectivity indexes (ID50 for cell growth/ED50 for VZV plaque inhibition) of BV-araU, BVDU, and Pry-araU were >1,000,000, 20,000, and >10,000, resp., while those of acyclovir and penciclovir ranged from 600 to 800. AraA was much less selective than any of the other drugs tested. The authors measured the amt. of [3H] thymidine incorporated into the acid-insol. fraction of VZV-infected cells to det. the ability of these drugs to selectively inhibit viral DNA synthesis. [3H]thymidine incorporation was markedly inhibited by all anti-VZV compds., except BVDU. Treatment of infected cells with drugs

from 32 to 38 h after infection inhibited the DNA synthesis to the same extent as VZV plaque formation. DNA synthesis in non-infected growing cells was inhibited to the same extent as cell growth. A particularly high selectivity index for the inhibition of DNA synthesis was noted for BV-araU, which was defined as the ratio of inhibition of DNA synthesis in VZV-infected and non-infected. The highest selectivity indexes were recorded for BV-araU > Pry-araU > acyclovir .gtoreq. penciclovir > AraA.

IT **77181-69-2**, Sorivudine
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(comparison of selectivity of anti-varicella-zoster virus nucleoside analogs)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 12 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:673540 HCAPLUS
DOCUMENT NUMBER: 123:74021
TITLE: Progress in the clinical management of herpesvirus infections
AUTHOR(S): Griffiths, P. D.
CORPORATE SOURCE: Sch. Med., Royal Free Hospital, London, NW3 2PF, UK
SOURCE: Antiviral Chemistry & Chemotherapy (1995), 6(4), 191-209
CODEN: ACCHEH; ISSN: 0956-3202
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

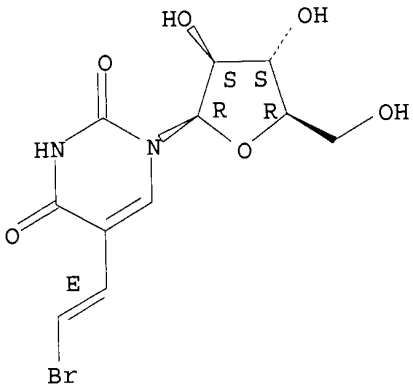
AB A review with 108 refs. Antiviral drug discovery has produced a series of drugs active against herpesviruses in vitro. Several of these are now licensed and/or have been used in clin. practice. This article reviews the mechanisms of action of acyclovir, ganciclovir, penciclovir, sorivudine and foscarnet, the development of resistance to these drugs and their pharmacokinetic and cellular toxicities. Based upon the natural histories of HSV, VZV and CMV, treatment objectives for each virus are discussed and the performance of each drug matched against these objectives. Overall, it is concluded that the perfect drug for treating herpesviruses does not exist, but that significant progress has been made

towards controlling several herpesvirus diseases. It is suggested that further progress will require not just improved drug discovery programs, but also an understanding of different pathogeneses and an appreciation by practising physicians that antiviral drugs must be given early in the infectious process to achieve the best results.

IT **77181-69-2**, Sorivudine
RL: ADV (Adverse effect, including toxicity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(progress in clin. management of herpesvirus infections)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 13 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:631038 HCAPLUS
DOCUMENT NUMBER: 123:102088
TITLE: Combination of azidothymidine (AZT) and (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) inhibits the replication of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) and varicella zoster virus (VZV) strains that are deficient in the expression of the viral thymidine kinase (TK)
AUTHOR(S): Andrei, G.; Snoeck, R.; Balzarini, J.; De Clercq, E.
CORPORATE SOURCE: Rega Inst. for Medical Res., Katholieke Univ. leuven, Louvain, B-3000, Belg.
SOURCE: Nucleosides & Nucleotides (1995), 14(3-5), 559-62
CODEN: NUNUD5; ISSN: 0732-8311
PUBLISHER: Dekker
DOCUMENT TYPE: Journal
LANGUAGE: English

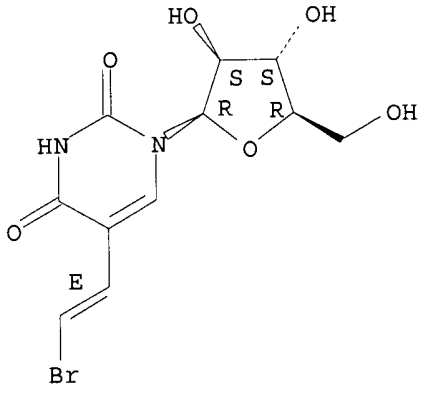
AB Combination of high concns. of AZT with BVDU, acyclovir (ACV) or ganciclovir (GCV) decreased their antiviral activity against TK+ HSV-1 but not TK+ VZV strains in cell cultures. When BVDU and AZT were used in combination against TK- HSV-1, TK- HSV-2 and TK- VZV strains, a pronounced inhibition of viral replication was obsd., whereas the drugs had no antiviral activity when used alone. This potentiating effect was not seen if AZT was combined with ACV or GCV.

IT **77181-69-2**, 1-.beta.-D-Arabinofuranosyl-(E)-5-(2-bromovinyl)uracil
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL

(Biological study); USES (Uses)
(combination of azidothymidine and (bromovinyl)deoxyuridine inhibits the replication in human cells of herpes simplex virus and varicella zoster virus strains that are deficient in the expression of the viral thymidine kinase)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 14 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:426687 HCAPLUS
DOCUMENT NUMBER: 123:102760
TITLE: Acyclovir derivatives and other nucleoside analogs for topical treatment of herpes infection
INVENTOR(S): Hostetler, Karl Y.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9426273	A1	19941124	WO 1993-US4450	19930512
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9343721	A1	19941212	AU 1993-43721	19930512
AU 701574	B2	19990204		
JP 08510236	T2	19961029	JP 1993-525361	19930512
EP 746319	A1	19961211	EP 1993-913832	19930512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

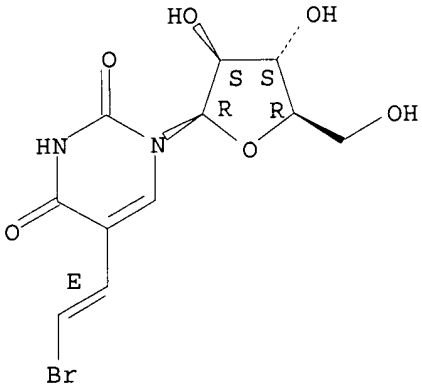
PRIORITY APPLN. INFO.: WO 1993-US4450 19930512

AB Compns. for topical use in herpes virus infections comprise anti-herpes nucleoside analog phosphate esters, e.g. acyclovir monophosphate and acyclovir diphosphate, which show increased activity against native strains of herpes virus as well as against resistant strains, particularly thymidine kinase neg. strains of virus. Also disclosed are methods for using the topical compns. in treatment of herpes disease.

IT **77181-69-2 77181-69-2D**, salts **87535-95-3 87535-95-3D**, salts
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(acyclovir derivs. and other nucleoside analogs for topical treatment of herpes infection)

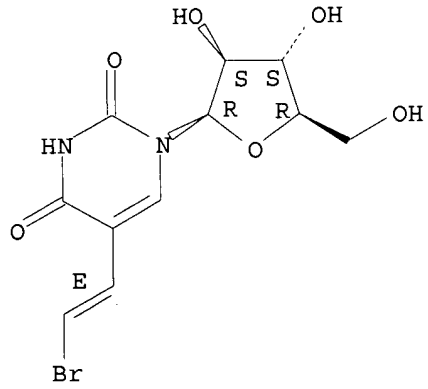
RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



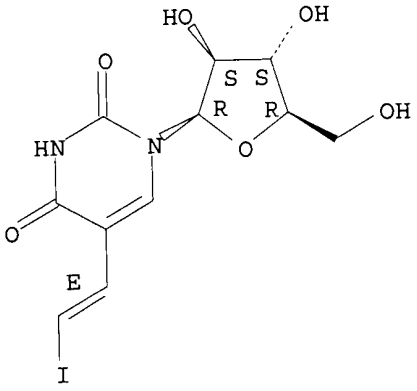
RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



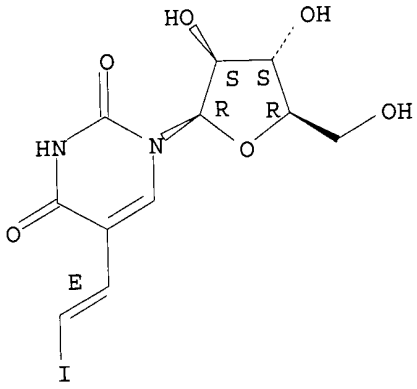
RN 87535-95-3 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-iodoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 87535-95-3 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-iodoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 15 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:426585 HCAPLUS
DOCUMENT NUMBER: 122:188170
TITLE: Preparation of peptide analog inhibitors of herpes viral ribonucleotide reductase.
INVENTOR(S): Deziel, Robert; Moss, Neil
PATENT ASSIGNEE(S): Bio-Mega/Boehringer Ingelheim Research Inc., Can.
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9420528	A1	19940915	WO 1994-CA106	19940228

W: AU, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KR, LV, NO, NZ, PL, RU, SK, UA

EP 618226	A1	19941005	EP 1994-102680	19940223
EP 618226	B1	20001129		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 197802	E	20001215	AT 1994-102680	19940223
ES 2152269	T3	20010201	ES 1994-102680	19940223
CA 2157196	AA	19940915	CA 1994-2157196	19940228
AU 9461516	A1	19940926	AU 1994-61516	19940228
AU 683450	B2	19971113		
BR 9406346	A	19960221	BR 1994-6346	19940228
CN 1118601	A	19960313	CN 1994-191343	19940228
HU 72894	A2	19960628	HU 1995-2570	19940228
JP 08507760	T2	19960820	JP 1994-519411	19940228
ZA 9401449	A	19941014	ZA 1994-1449	19940302
FI 9504048	A	19950829	FI 1995-4048	19950829
NO 9503437	A	19950901	NO 1995-3437	19950901
LV 11037	B	19960620	LV 1995-268	19950901
PRIORITY APPLN. INFO.:			US 1993-25540 A	19930303
			WO 1994-CA106 W	19940228

OTHER SOURCE(S): MARPAT 122:188170

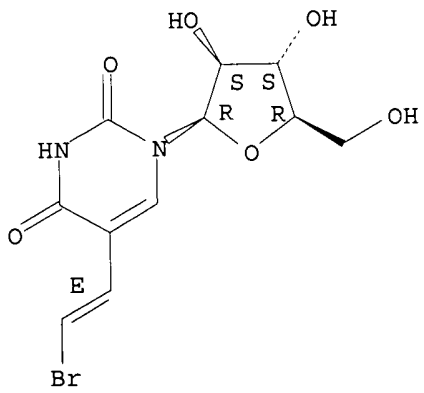
AB A-B-D-NHCH(CH2COR1)CONHCH(CR2R3COOH)COE [A = disubstituted lower alkanoyl where the substituents are selected from Ph or monosubstituted Ph where the substituent = alkyl, halo, OH, alkoxy; B = NMeCHR4CO; R4 = alkyl; D = NMeCHR5CO; R5 = (substituted) alkyl; R1 = alkyl, cycloalkyl, alkylcycloalkyl, mono- or disubstituted amino; R2 = H, alkyl; R3 = alkyl; R2R3C = cycloalkyl; E = NHR8, NHCHR9Z; R8, R9 = alkyl, (alkyl)cycloalkyl, etc.; Z = CH2OH, CO2H, CONH2, CO2R10; R10 = alkyl], were prepd. Thus, (PhCH2)2CHCO-NMeVal-Tbg-Asp(pyrrolidino)-Asp(cyPn)-.gamma.MeLeucinol [NMeVal = (S)-3-methyl-2-(methylamino)butanoate; Tbg = (S)-2-amino-3,3-dimethylbutanoate; Asp(cyPn) = (S)-.alpha.-amino-1-carboxycyclopentaneacetate; .gamma.MeLeucinol = (S)-2-amino-4,4-dimethylpentanol], prepd. by soln. phase methods, inhibited HSV-1 ribonucleotide reductase with IC50 = 0.17 .mu.M.

IT **77181-69-2**, Brovavir
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(treatment of herpes infections with peptide analog ribonucleotide reductase inhibitors and antiviral nucleosides)

RN 77181-69-2 HCAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 16 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:339471 HCAPLUS
DOCUMENT NUMBER: 122:230755
TITLE: Method of combating acyclovir-resistant herpes simplex viral infections using peptide derivatives, and preparation of the peptide derivatives
INVENTOR(S): Chafouleas, James Gus; Deziel, Robert
PATENT ASSIGNEE(S): Bio-Mega/Boehringer Ingelheim Research Inc., Can.
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9425046	A1	19941110	WO 1994-CA242	19940429
W: AU, BR, BY, CN, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2095408	AA	19941104	CA 1993-2095408	19930503
AU 9466423	A1	19941121	AU 1994-66423	19940429
AU 683465	B2	19971113		
BR 9406575	A	19960319	BR 1994-6575	19940429
CN 1126438	A	19960710	CN 1994-192662	19940429
HU 73779	A2	19960930	HU 1995-3135	19940429
JP 08509476	T2	19961008	JP 1994-523705	19940429
EP 767671	A1	19970416	EP 1994-914991	19940429
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
NO 9504390	A	19960102	NO 1995-4390	19951102
PRIORITY APPLN. INFO.:			CA 1993-2095408	19930503
			WO 1994-CA242	19940429

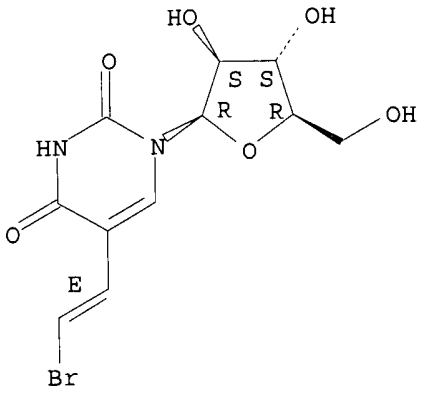
OTHER SOURCE(S): MARPAT 122:230755

AB A method is disclosed for treating acyclovir-resistant herpes infections in a mammal. The method comprises administering a peptide deriv. (Markush included), or a combination of the peptide deriv. and an antiviral nucleoside analog, to the infected mammal. Peptide deriv. prepn., as well as prepn. of intermediates, is included. Results demonstrated that a peptide deriv. of the invention was active against wild-type HSV-1 and exhibited similar efficacy against acyclovir-resistant HSV-1. Data for synergism (with acyclovir) are also presented.

IT **77181-69-2**, Brovavir **77181-69-2D**, Brovavir, peptide deriv. mixts.
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(acyclovir-resistant herpes simplex infection treatment with peptide derivs. with optional antiviral nucleoside analog, and prepn. of the peptide derivs.)

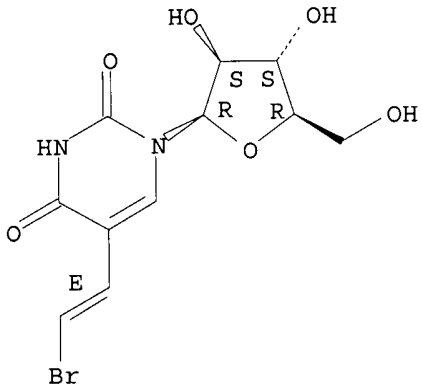
RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



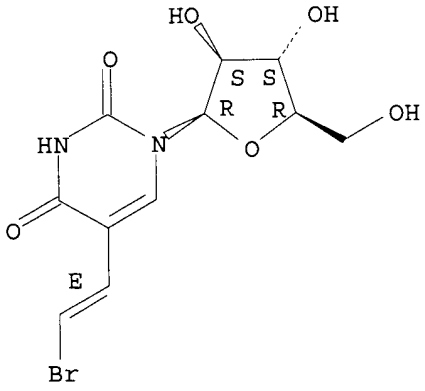
L43 ANSWER 17 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:231584 HCAPLUS
DOCUMENT NUMBER: 122:71408
TITLE: In vitro and in vivo anti-herpes viral activities and biological properties of CV-araU
AUTHOR(S): Ashida, Noriyuki; Sakata, Shinji; Kano, Fumitaka; Nishitani, Makiko; Watanabe, Yohko; Machida, Haruhiko
CORPORATE SOURCE: Biology Laboratory, R. and D. Division, Yamasa Corporation, 10-1, Araoicho 2-chome, Choshi, 288, Japan
SOURCE: Antiviral Research (1994), 25(3-4), 179-84
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We compared the in vitro and in vivo antiviral effects against herpes simplex virus type 1 (HSV-1) and other biol. properties of 1-.beta.-D-arabinofuranosyl-5-[(E)-2-chlorovinyl]uracil (CV-araU) and 1-.beta.-D-arabinofuranosyl-5-[(E)-2-bromovinyl]uracil (BV-araU,

sorivudine). Both CV-araU and BV-araU exhibited antiviral activities against HSV-1 in the cell culture derived from mouse, though the activities were lower than those seen in human cells. For i.p. and intracerebral infections in mice with HSV-1 strain WT-51, both compds., administered twice daily, were effective in increase in the survival rate at doses of 15 mg/kg and 30 mg/kg, resp. In pharmacokinetic anal., both drugs were absorbed well in the rat gastrointestinal tract following oral administration. There was no difference between the metab. of orally administered CV-araU and BV-araU in rats. High levels of the corresponding base were found in plasma after oral administration of CV-araU and BV-araU, but much lower base levels were seen after i.v. doses. Both drugs were resistant to degrdn. by rat liver enzymes.

IT **77181-69-2 77181-70-5**
RL: **BAC (Biological activity or effector, except adverse)**; BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(comparative anti-herpes viral activities, pharmacokinetics, and metab. of arabinofuranosylchlorovinyluracil and arabinofuranosylbromovinylurac il)

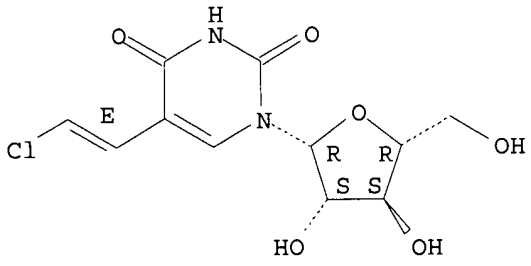
RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 77181-70-5 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-chloroethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



Searched by Thom Larson, STIC, 308-7309

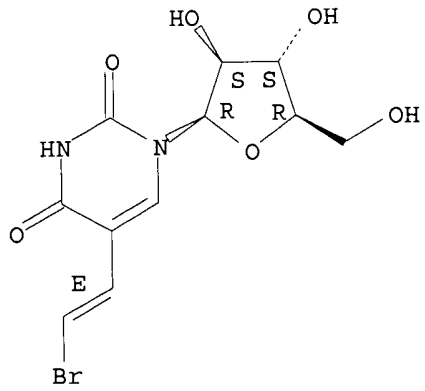
L43 ANSWER 18 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:141289 HCAPLUS
DOCUMENT NUMBER: 123:160129
TITLE: A sensitive assay system screening antiviral compounds against herpes simplex virus type 1 and type 2
AUTHOR(S): Sudo, Kenji; Konno, Kenji; Yokota, Tomoyuki; Shigeta, Shiro
CORPORATE SOURCE: Rational Drug Design Laboratories, Fukushima, 960-12, Japan
SOURCE: Journal of Virological Methods (1994), 49(2), 169-78
CODEN: JVMEDH; ISSN: 0166-0934
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A highly sensitive and accurate assay system was developed for in vitro evaluation of anti-herpes simplex virus (anti-HSV) agents using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and human embryonic lung fibroblast (MRC-5) cells. This assay system was highly sensitive for both HSV-1 and -2. Confluent MRC-5 cells were infected with either HSV-1 KOS strain or HSV-2 G strain of 25 TCID50 in the presence of various concns. of test compds. The optical d. of formazan was used to det. cell viability. The EC50 values of acyclovir and several other anti-HSV agents were similar to those obtained by the plaque redn. method. This MTT assay is useful for screening anti-HSV-1 and -2 agents.

IT **77181-69-2**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(assay system for screening antiviral compds. against herpes simplex virus types 1 and 2)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 19 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:645211 HCAPLUS
DOCUMENT NUMBER: 121:245211
TITLE: Retinal toxicity and ocular kinetics of

1-.beta.-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil in rabbits

AUTHOR(S): Mochizuki, Kiyofumi; Torisaki, Makoto; Yamashita, Yohko; Komatsu, Masaki; Tanahashi, Toshiro; Ijichi, Katsushi; Machida, Haruhiko

CORPORATE SOURCE: Sch. Med., Kanazawa Univ., Kanazawa, 920, Japan

SOURCE: Graefe's Archive for Clinical and Experimental Ophthalmology (1994), 232(8), 503-8
CODEN: GACODL; ISSN: 0721-832X

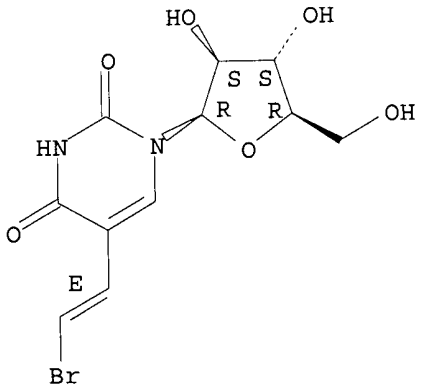
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The intraocular penetration of 1-.beta.-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil (BV-araU), a new antiviral drug, after oral administration, the effects of non-toxic intravitreal doses of BV-araU, and the intraocular kinetics of BV-araU after intraocular injection were studied in rabbits. The intravitreal penetration of BV-araU after oral administration was very poor: 0.11 .+-. 0.13 .mu.g/mL and 0.20 .+-. 0.02 .mu.g/mL, resp., in albino and pigmented rabbits 2 h after 30 mg/kg. An intravitreal injection of 200 .mu.g BV-araU caused transient electroretinog. (ERG) changes, whereas a 100-.mu.g injection and intravitreal irrigation with 20 .mu.g/mL BV-araU or an intravitreal irrigating soln. contg. 20 .mu.g/mL BV-araU is nontoxic to the retina and may be used for treatment of retinitis caused by varicella-zoster virus or herpes simplex virus type 1.

IT **77181-69-2**, BV-araU
RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(ocular pharmacokinetics and toxicity of BV-araU for treatment of retinitis)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 20 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:524571 HCAPLUS
DOCUMENT NUMBER: 121:124571
TITLE: Structure-Activity Study on Antiviral 5-Vinylpyrimidine Nucleoside Analogs Using Wiener's Topological Index

Searched by Thom Larson, STIC, 308-7309

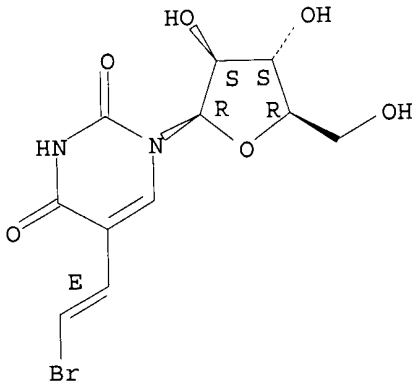
AUTHOR(S): Mendiratta, Seema; Madan, A. K.
CORPORATE SOURCE: College of Pharmacy, University of Delhi, New Delhi, 110 017, India
SOURCE: Journal of Chemical Information and Computer Sciences (1994), 34(4), 867-71
CODEN: JCISD8; ISSN: 0095-2338
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The relationship between Wiener's topol. index and the antiviral activity of a series of 5-vinylpyrimidine nucleoside analogs has been investigated. Values for more than 100 compds. were computed, and an active range was identified. The predicted activity of each compd. was compared with reported antiviral activity against herpes simplex virus type I. Due to significant correlation between antiviral activity and Wiener's topol. index, it was possible to predict antiviral activity with an accuracy of .apprx.83%.

IT **77181-69-2 77181-70-5**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(virucidal activity of, against herpes simplex virus type I, Wiener's topol. index and structure in relation to)

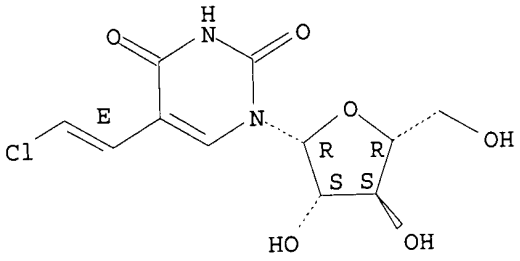
RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 77181-70-5 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-chloroethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



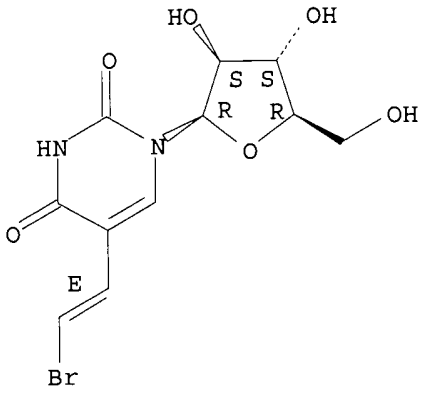
L43 ANSWER 21 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:449642 HCAPLUS
DOCUMENT NUMBER: 121:49642
TITLE: 5'-O-alkyl and acyl prodrugs of 1-.beta.-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil
AUTHOR(S): Kano, F.; Ijichi, K.; Ashida, N.; Watanabe, Y.; Sakata, S.; Machida, H.
CORPORATE SOURCE: R and D Div., Yamasa Corp., Choshi, 288, Japan
SOURCE: Antiviral Chem. Chemother. (1994), 5(2), 74-82
CODEN: ACCHEH; ISSN: 0956-3202
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 5'-O-alkyl derivs. of a-.beta.-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil (BV-araU) were prepd. by selective alkylation and deprotection of 2',3'-bis-O-tetrahydropyranyl BV-araU to enhance metabolic stability and evaluated for efficacy as oral prodrugs of BV-araU. For comparison, their acyl congeners, and 3'-O- and 2'-O-ethyl-BV-araU, were also prepd. by direct acylation of BV-araU and by selective protection, alkylation, and deprotection, resp. The 5'-O-alkyl prodrugs were stable in acidic solns., whereas the 5'-O-acyl analogs were unstable under the same conditions. When incubated with enterobacteria, the 5'-O-acyl derivs. resulted in the formation of BV-uracil through non-enzymic hydrolysis of BC-araU, but the 5'-O-alkyl prodrugs did not. 5'-O-Short-chain aliph. alkyl (not longer than butyl) and generally acyl prodrugs gave higher blood concns. of BV-araU than the arom. derivs. Plasma concns. of BV-araU were equal or slightly higher than those after equiv. oral dose of BV-araU. 5'-O-ethyl-BV-araU was effective against intracerebral, i.p., and cutaneous infections with herpes simplex virus type 1 in mice.

IT **77181-69-2DP**, alkyl and acyl derivs. **147266-23-7P**
RL: **BAC (Biological activity or effector, except adverse)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(prepn. and antiviral activity of, against HIV-1 virus)

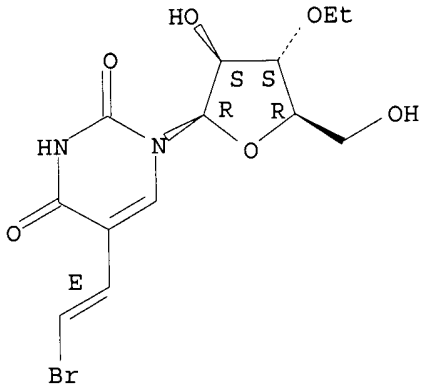
RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 147266-23-7 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 5-(2-bromoethenyl)-1-(3-O-ethyl-.beta.-D-arabinofuranosyl)-, (E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 22 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:449467 HCAPLUS
DOCUMENT NUMBER: 121:49467
TITLE: Sorivudine: A new antiviral drug specifically active against herpes simplex virus type 1 and varicella-zoster
AUTHOR(S): Rabasseda, Xavier; Mealy, Nancy; Machida, Haruhiko
CORPORATE SOURCE: Med. Inf. and Doc. Dep., J.R. Prous Sci. Publ., Barcelona, Spain
SOURCE: Med. Actual. (1993), 29(8), 555-47
CODEN: MDACAP; ISSN: 0025-7656
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 61 refs. Sorivudine is a new antiviral nucleoside analog which has shown potent and selective activity against herpes simplex virus type 1 and varicella-zoster virus strains in vitro and vivo tests. Sorivudine is more active than acyclovir against varicella-zoster virus, currently the treatment of choice for herpesvirus infections in humans, while showing a high virus/cell selectivity ratio. Toxicity data and the

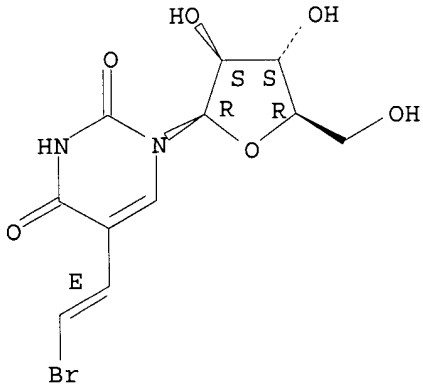
experience with sorivudine in clin. practice indicate a remarkable safety margin for this drug, which is given p.o. on a three-times-daily schedule according to pharmacokinetic evaluations unless concomitantly administered with fluorinated anticancer drugs. The high clin. efficacy of sorivudine against herpes zoster suggests that it will be an important and frequently used drug in the near future.

IT **77181-69-2**, Sorivudine
RL: **BAC (Biological activity or effector, except adverse)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antiviral activity of)

RN 77181-69-2 HCAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 23 OF 37 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:400273 HCAPLUS
DOCUMENT NUMBER: 121:273
TITLE: antiviral activity of 1-.beta.-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil against thymidine kinase negative strains of varicella-zoster virus
AUTHOR(S): Kawai, Hideki; Yoshida, Itsuro; Suzutani, Tatsuo
CORPORATE SOURCE: Dep. Microbiol., Asahikawa Med. Coll., Asahikawa, 078, Japan
SOURCE: Microbiology and Immunology (1993), 37(11), 877-82
CODEN: MIIMDV; ISSN: 0385-5600
DOCUMENT TYPE: Journal
LANGUAGE: English

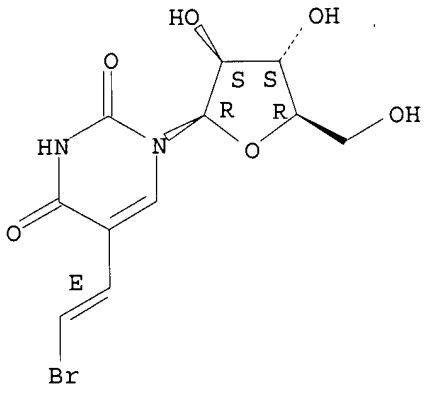
AB Mechanism of antiviral activity of 1-.beta.-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil (BV-araU) against the YSR strain of varicella-zoster virus (VZV), which is a mutant derived from the wild YS strain and is completely deficient in viral thymidine kinase (TK), was searched in comparison with antiviral activity of other thymidine analogs, guanosine analog and thymidylate synthase (TS) inhibitor in human embryo lung fibroblast cells. Thymidine analogs, such as BV-araU, 5-iododeoxyuridine (IUDR), 1-.beta.-D-arabinofuranosylthymine (araT), and guanosine analog, such as 9-(2-hydroxyethoxymethyl)guanine (ACV), showed higher antiviral activity to the YS strain than to the YSR strain. Though, BV-araU also had the antiviral activity of a microgram level against the YSR strain. In contrast to these results, TS inhibitor, 5-fluorodeoxyuridine (FUDR), had higher antiviral activity to the YSR strain than to the YS strain.

Highly synergistic antiviral activities of FUDR to the YS strain and the YSR strain were obsd. in combination with IUDR, araT, or ACV. However, weakly synergistic or additive inhibition to the YSR strain was shown in combination of BV-araU and FUDR, in spite of highly synergistic effect of this combination to the YS strain. The viral and cellular TS activity was partially inhibited by BV-araU monophosphate, but not by BV-araU. These results indicate that BV-araU is converted into BV-araU monophosphate by cellular TK, and the inhibition of TS activity by BV-araU monophosphate in the YSR strain-infected cells results in the suppression of viral replication.

IT **77181-69-2**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antiviral activity of, against thymidine kinase-neg. strains of varicella-zoster virus)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

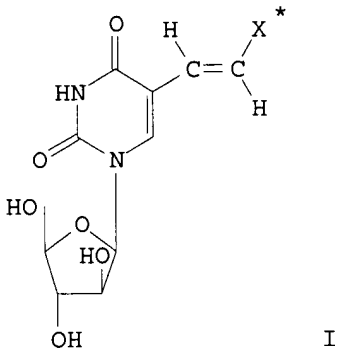


L43 ANSWER 24 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:218429 HCAPLUS
DOCUMENT NUMBER: 120:218429
TITLE: Process for preparing no-carrier-added radiohalogenated vinylnucleosides
INVENTOR(S): Dougan, Alfred Hayes
PATENT ASSIGNEE(S): Triumf, Can.
SOURCE: U.S., 10 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5248771	A	19930928	US 1991-721383	19910626
US 5422345	A	19950606	US 1993-91021	19930714

PRIORITY APPLN. INFO.: US 1991-721383 19910626
OTHER SOURCE(S): CASREACT 120:218429; MARPAT 120:218429

GI



I

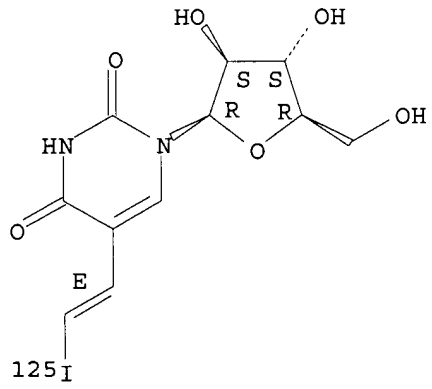
AB The title compds. [X*]XVaraU (I; X* = radiohalogen), useful for diagnosis and treatment of infection with herpes simplex virus (HSV) type 1 and HSV encephalitis, are prepd. by reacting [X*]X- (X* = radioactive halogen) with with YVaraU (Y = second halogen) in the presence of a cuprous ion catalyst under anaerobic and reducing conditions. Thus, a soln. of 1.5 mg (E)-5-(2-bromovinyl)-.beta.-D-arabinofuranosyluracil and 12 mg of a mixt. (obtained by mixing 30 mg CuSO4.5H2O, 2.0 g ascorbic acid, and 100 mg SnSO4) in aq. 0.01 M H2SO4 was injected into 14 .mu.L of a soln. of [125I]NaI in 0.1 N NaOH in the conical vial, subsequently flushed with N(g) for 1 min, and heated for 60 min in a heating block at 95.degree. to give, after purifn. with A Waters SEP-PAK (T.M) C1-8 cartridge and HPLC using a Phenomenex Bond clone column, 87.7% I (X* = 125I) (II) with 93.3% radiochem. purity. I (X* = 123I) of 94.0% radiochem. purity was also prepd. The biodistribution of II in the bodies of mice infected with HSV throughout the entire body showed that the brain uptake of II was 36.2 times that of the noninfected mice after 48 h.

IT **128187-92-8P 128188-08-9P**
RL: SPN (Synthetic preparation); **PREP (Preparation)**
(prepn. of, for diagnosis of encephalitis from herpes simplex virus)

RN 128187-92-8 HCAPLUS

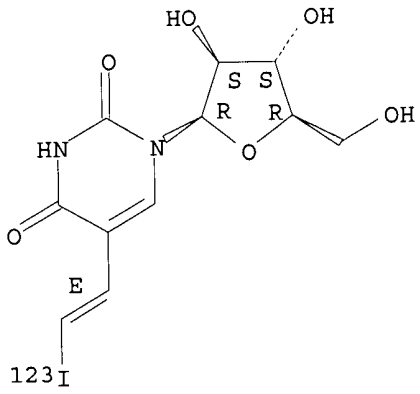
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-(iodo-125I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 128188-08-9 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-(iodo-123I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



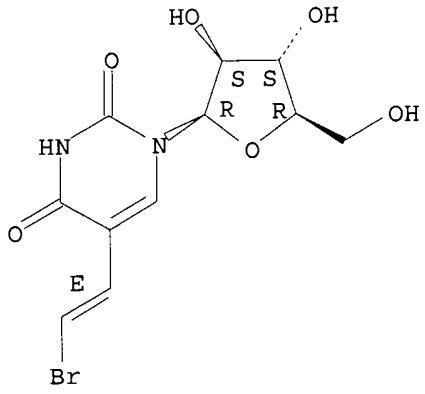
L43 ANSWER 25 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:400264 HCAPLUS
DOCUMENT NUMBER: 119:264
TITLE: In vitro anti-herpesvirus activities of 5-substituted 2'-deoxy-2'-methylidene pyrimidine nucleosides
AUTHOR(S): Machida, H.; Sakata, S.; Ashida, N.; Takenuki, K.; Matsuda, A.
CORPORATE SOURCE: Biol. Lab., Yamasa Shoyu Co., Ltd., Chosi, 288, Japan
SOURCE: Antiviral Chemistry & Chemotherapy (1993), 4(1), 11-17
CODEN: ACCHEH; ISSN: 0956-3202
DOCUMENT TYPE: Journal
LANGUAGE: English

AB New pyridine deoxyribonucleoside analogs, 2'-deoxy-2'-methylideneuridine (DMDU), 2'-deoxy-2'-methylidenecytidine (DMDC), and their 5-substituted derivs. were tested for the anti-herpesvirus activities and anti-proliferative activity. E-5-(2-Bromovinyl)uracil deriv. (BV-DMDU) and its cytosine congener were synthesized from 1-.beta.-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil (BV-araU). 5-Bromo, 5-iodo, 5-Me, and 5-Et derivs. of DMDU and BV-DMDU showed activities against herpes simplex virus type 1 (HSV-1) and varicella-zoster virus (VZV). The corresponding DMDC derivs. had no or only weak antiviral activity. Among the 2'-deoxy-2'-methylidene pyrimidine nucleosides, BV-DMDU showed the most potent and selective anti-VZV activity. BV-DMDU was more potent than acyclovir, but less active than BV-araU. BV-DMDU was inactive against human diploid and tumor cells. DMDC and F-DMDC (5-fluoro deriv.) were potent inhibitors of HSV-1, herpes simplex virus type 2, VZV, and human cytomegalovirus (HCMV) and also had significant anti-proliferative activity. Their potency against HCMV was better than that of ganciclovir and araC. Some DMDU derivs. also showed anti-HCMV activity, but they had anti-proliferative activity. The anti-HCMV activity of these DMDC and DMDU compds. was generally more potent than those against HSV-1 and VZV thereof, suggesting the participation of cellular kinase in their antiviral action.

IT **77181-69-2P**
RL: SPN (Synthetic preparation); **PREP (Preparation)**
(prepn. and protection of, with tetraisopropyldisiloxane)

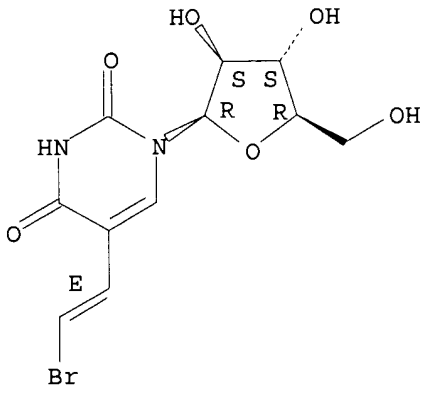
RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 26 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:462163 HCAPLUS
DOCUMENT NUMBER: 117:62163
TITLE: Comparison of antiviral assay methods using cell-free and cell-associated varicella-zoster virus
AUTHOR(S): Shiraki, Kimiyasu; Ochiai, Hiroshi; Namazue, Junko; Okuno, Toshiomi; Ogino, Satoshi; Hayashi, Kyoko; Yamanishi, Koichi; Takahashi, Michiaki
CORPORATE SOURCE: Dep. Virol., Toyama Med. Pharm. Univ., Toyama, 930-01, Japan
SOURCE: Antiviral Research (1992), 18(2), 209-14
CODEN: ARSRDR; ISSN: 0166-3542
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Assay methods for varicella-zoster virus (VZV) susceptibility to acyclovir (ACV) of VZV were compared by using cell-free (CF) and cell-assocd. (CA) virus of 6 .times. plaque-purified VZV. The 50% EDs (ED50) of ACV, as required to reduce virus plaque formation by 50%, were about 8 times higher for CA virus than for CF virus. Also, the ED50 of 1-.beta.-D-arabinofuranosyl-(E)-5-(2-bromovinyl)uracil (BVaraU) for CA-VZV was higher than for CF-VZV, and fresh clin. isolates of VZV gave higher ACV ED50 values than CF virus. CA virus prepd. at various times after CF virus infection showed a gradual increase of the ACV ED50 with time, ranging from the ED50 for CF virus to that for CA virus.
IT **77181-69-2**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antiviral activity of, evaluation of, in cell-free and human cell-assocd. varicella-zoster virus assay)
RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



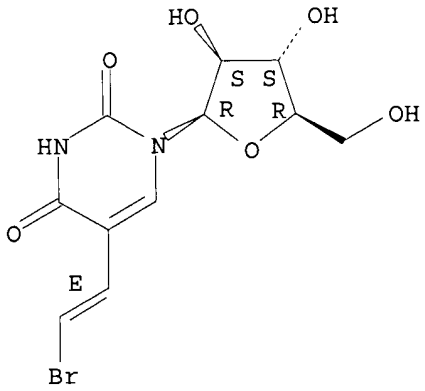
L43 ANSWER 27 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:622855 HCAPLUS
DOCUMENT NUMBER: 115:222855
TITLE: Inhibition of DNA synthesis in varicella-zoster virus-infected cells by BV-araU
AUTHOR(S): Machida, Haruhiko; Watanabe, Yoko
CORPORATE SOURCE: Res. Dev. Div., Yomatsa Shoyu Co., Ltd., Choshi, Japan
SOURCE: Microbiology and Immunology (1991), 35(2), 139-45
CODEN: MIIMDV; ISSN: 0385-5600
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The inhibitory effect of BV-araU on DNA synthesis in human embryonic lung cells infected with varicella-zoster virus (VZV) or herpes simplex virus type 1 (HSV-1) was compared with that of acyclovir. Cellular uptake of [3H]thymidine and its incorporation into DNA was markedly stimulated by the infection with VZV or HSV-1, suggesting that the incorporation was mainly due to viral DNA synthesis. DNA synthesis in VZV-infected cells was dose-dependently suppressed by BV-araU and acyclovir, although cellular uptake of [3H]thymidine decreased in cells treated with a high concn. of drugs for an extended time. DNA synthesis in HSV-1-infected cells was also markedly inhibited by both drugs in a dose-dependent manner, without affecting cellular uptake of [3H]thymidine. The concn. of drugs inhibiting DNA synthesis was well correlated to their in vitro anti-VZV and anti-HSV-1 activities. The inhibitory concn. of BV-araU for DNA synthesis in VZV-infected cells was one-thousandth of that of acyclovir. These results suggest that the antiviral action of BV-araU against VZV and HSV-1 is based on the inhibition of DNA synthesis in herpesvirus-infected cells.

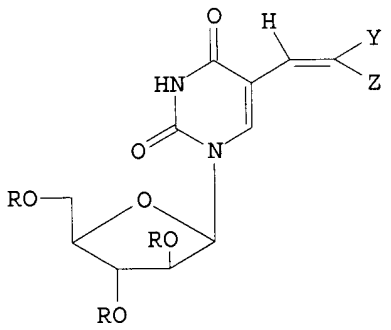
IT **77181-69-2**, 1-.beta.-D-Arabinofuranosyl-E-5-(2-bromovinyl)uracil
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antiviral activity of, against herpes simplex virus type 1 and Varicella-Zoster virus, DNA formation inhibition in relation to)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 28 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:450182 HCAPLUS
DOCUMENT NUMBER: 115:50182
TITLE: Nucleic acid related compounds. 65. New syntheses of 1-(.beta.-D-arabinofuranosyl)-5(E)-(2-iodovinyl)uracil (IVAraU) from vinylsilane precursors. Radioiodine uptake as a marker for thymidine kinase herpes viral infections
AUTHOR(S): Robins, Morris J.; Manfredini, Stefano; Wood, Steven G.; Wanklin, R. James; Rennie, Bruce A.; Sacks, Stephen L.
CORPORATE SOURCE: Dep. Chem., Brigham Young Univ., Provo, UT, 84602, USA
SOURCE: Journal of Medicinal Chemistry (1991), 34(7), 2275-80
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB (Trimethylsilyl)acetylene was coupled with 1-(2,3,5-tri-O-acetyl-.beta.-D-arabinofuranosyl)-5-iodouracil to give 1-(2,3,5-tri-O-acetyl-.beta.-D-arabinofuranosyl)-5-[2-(trimethylsilyl)ethynyl]uracil which underwent Lindlar hydrogenation to give 1-(2,3,5-tri-O-acetyl-.beta.-D-arabinofuranosyl)-5(Z)-[2-(trimethylsilyl)vinyl]uracil I. Treatment of I with ICl (or NaI-PhICl2) in benzene gave 1-(2,3,5-tri-O-acetyl-.beta.-D-arabinofuranosyl)-5(E)-(2-iodovinyl)uracil, whereas polar solvents favored the (Z)-iodovinyl isomer. Deacetylation of the E-isomer gave

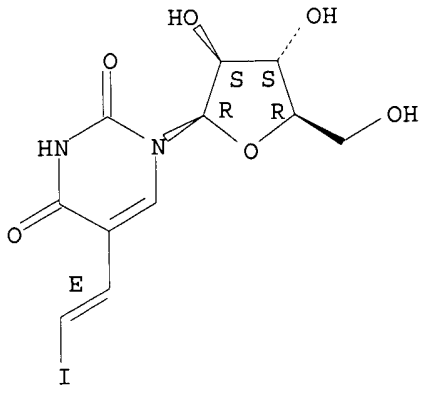
1-(.beta.-D-arabinofuranosyl)-5(E)-(2-iodovinyl)uracil (IVAraU). A microscale in situ synthesis with Na125I gave [125I]IVAraU. Treatment of HSV-infected cells with [125I]IVAraU resulted in virus-dependent uptake assocd. with nucleoside phosphorylation by wild type or acyclovir-resistant DNA polymerase mutants (but not with TK- HSV-1 mutants). Uptake was virus-inoculum dependent and was detectable within 4 h postinfection. The process was not completely reversible. Virus-specified uptake of [125I]IVAraU may allow automated in vitro detection of HSV isolates.

IT **87535-95-3P**
RL: SPN (Synthetic preparation); **PREP (Preparation)**
(prepn. and labeling by iodine-125)

RN 87535-95-3 HCAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-iodoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 29 OF 37 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1991:200600 HCAPLUS

DOCUMENT NUMBER: 114:200600

TITLE: Analysis of mutations in the thymidine kinase genes of drug-resistant varicella-zoster virus populations using the polymerase chain reaction

AUTHOR(S): Lacey, S. F.; Suzutani, T.; Powell, K. L.; Purifoy, D. J. M.; Honess, R. W.

CORPORATE SOURCE: Div. Virol., Natl. Inst. Med. Res., London, NW7 1AA, UK

SOURCE: Journal of General Virology (1991), 72(3), 623-30
CODEN: JGVIAY; ISSN: 0022-1317

DOCUMENT TYPE: Journal

LANGUAGE: English

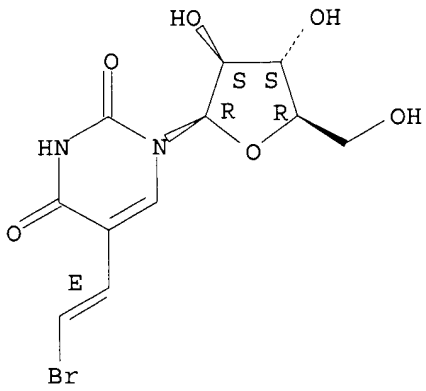
AB The polymerase chain reaction (PCR) technique was used to analyze mutations in the thymidine kinase (TK) gene of varicella-zoster virus (VZV) assocd. with resistance to the 5-bromovinyl (BVaraU) and 5-propynyl (PYaraU) analogs of arabinofuranosyl deoxyuridine. The results from this study allow 3 clear conclusions to be drawn. Firstly, the technique clearly shows that populations of VZV derived from plaque purifn. were truly clonal only when the plaques were initiated from cell-free virus (representing a tiny fraction of infectious virus) and plaques initiated by infected cells contained a mixt. of variants. Secondly, despite the background mutations caused by errors of the Taq DNA polymerase, mutations

relevant to drug resistance can easily be distinguished. The BVaraU-resistant mutant, 7-1, contained an aspartic acid to asparagine mutation at residue 18 and a single base deletion (position 65,298 of the VZV DNA sequence), resulting in a frameshift and premature termination of the polypeptide chain, was found in the BVaraU-resistant mutant YSR. PYaraU-resistant virus populations contained viruses with 2 or more of 3 independent mutations, i.e. single base substitutions resulting in mutations from leucine to proline at residue 92, histidine to arginine at residue 97, and a deletion of 20bp (residues 65,135 to 65,154). Finally, the technique has uncovered novel sites in the virus TK assocd. with drug resistance. Thus, in vitro amplification using the PCR combined with cloning and sequencing is a relatively rapid method for identifying mutations in small virus populations even when they are not homogeneous.

IT **77181-69-2**
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(varicella-zoster virus thymidine kinase gene mutation conferring resistance to, polymerase chain reaction for anal. of)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 30 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:584252 HCAPLUS
DOCUMENT NUMBER: 113:184252
TITLE: Comparative activities of several nucleoside analogs against duck hepatitis B virus in vitro
AUTHOR(S): Yokota, Tomoyuki; Konno, Kenji; Chonan, Eiko; Mochizuki, Shinobu; Kojima, Kana; Shigeta, Shiro; De Clercq, Erik
CORPORATE SOURCE: Dep. Bacteriol., Fukushima Med. Coll., Fukushima, 960-12, Japan
SOURCE: Antimicrobial Agents and Chemotherapy (1990), 34(7), 1326-30
CODEN: AMACCQ; ISSN: 0066-4804
DOCUMENT TYPE: Journal
LANGUAGE: English

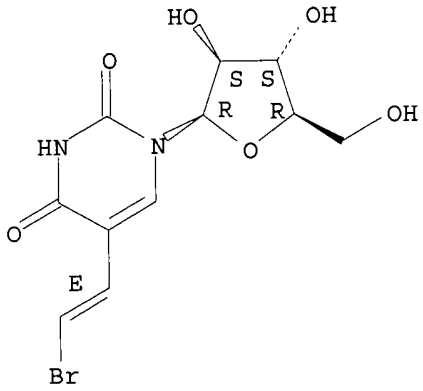
AB Duck hepatitis B virus (DHBV) replication in primary duck hepatocytes was monitored by examg. the synthesis of both DHBV DNA and DHBV core antigen. Several nucleoside analogs which were previously shown to inhibit the

replication of DNA viruses (i.e., herpesviruses) and retroviruses were examd. for their inhibitory effects on the synthesis of DHBV core antigen in primary duck hepatocytes. (S)-9-(3-Hydroxy-2-phosphonylmethoxypropyl)adenine [(S)-HPMPA], 9-(2-phosphonylmethoxyethyl)-2,6-diaminopurine, 2',3'-dideoxyadenosine, and 2',3'-dideoxycytidine inhibited DHBV core antigen synthesis at concns. that were lower than those found to be toxic to the primary hepatocytes. Of all the compds. tested, (S)-HPMPA showed the lowest 50% effective concn. (0.5 .mu.g/mL). The selectivity index or ratio of the 50% cytotoxic concn. to the 50% effective concn. of (S)-HPMPA was greater than 300. (S)-HPMPA not only inhibited DHBV core antigen but also DHBV DNA synthesis in DHBV-infected hepatocytes.

IT **77181-69-2**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antiviral activity of, against duck hepatitis B virus)

RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 31 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:232459 HCAPLUS
DOCUMENT NUMBER: 112:232459
TITLE: In vitro anti-herpes virus action of a novel antiviral agent, brovavir (BV-araU)
AUTHOR(S): Machida, Haruhiko
CORPORATE SOURCE: Res. Dev. Div., Yamasa Shoyu Co., Ltd., Choshi, 288, Japan
SOURCE: Chemotherapy (Tokyo) (1990), 38(3), 256-61
CODEN: NKRZAZ; ISSN: 0009-3165
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB The antiviral action of 1-.beta.-arabinofuranosyl-E-5-(2-bromovinyl) uracil(brovavir) on herpes simplex virus type 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV) and human cytomegalovirus by a plaque redn. method on human embryo lung cells was examd. Acyclovir, bromovinyl-2'-deoxyuridine, idoxuridine and vidarabine(areA) were used as control drugs. Brovavir exhibited extremely marked antiviral activity against all 5 strains of VZV and significant activity against all 7

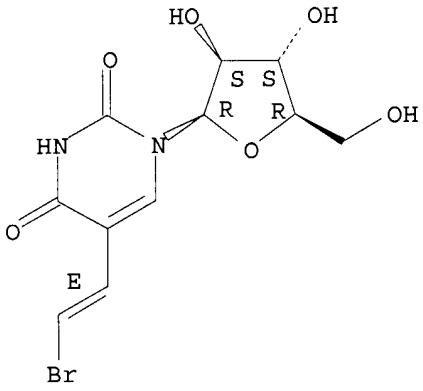
strains of HSV-1. Av. ED50 values of brovavir for VZV AND HSV-1 were 0.4 and 22 ng/mL, resp. Brovavir was most potent against VZV and HSV-1 of the antiviral drugs tested. Based on the ED50 value, brovavir was over 2,000 times more active than acyclovir, and about 4000 times more active than vidarabine against VZV. On the other hand, brovavir showed marginal or no effect on HSV-2 plaque formation and little effect on human cytomegalovirus, suggesting that brovavir is a potential candidate for clin. application as a novel antiherpes drug in the treatment of HSV-1 and VZV infections, particularly herpes zoster.

IT **77181-69-2**, Brovavir
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(antiviral action of, on herpes simplex 1 and varicella-zoster virus)

RN 77181-69-2 HCAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 32 OF 37 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1989:147255 HCAPLUS

DOCUMENT NUMBER: 110:147255

TITLE: Low levels of herpes simplex virus thymidine-thymidylate kinase are not limiting for sensitivity to certain antiviral drugs or for latency in a mouse model

AUTHOR(S): Coen, Donald M.; Irmiere, Alice F.; Jacobson, Jennie G.; Kerns, Kelvin M.

CORPORATE SOURCE: Dep. Biol. Chem. Mol. Pharmacol., Harvard Med. Sch., Boston, MA, 02115, USA

SOURCE: Virology (1989), 168(2), 221-31
CODEN: VIRLAX; ISSN: 0042-6822

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Herpes simplex virus mutant KG111 contains a nonsense mutation at codon 44 of the viral thymidine kinase (tk) gene and produces low amts. of a truncated tk polypeptide. The authors tested mutant KG111 and related viruses that specify varying amts. of similar truncated tk polypeptides for their sensitivities to antiviral nucleoside analogs at different temps. using plaque redn. assays. The nonsense mutation confere high resistance to bromovinyldeoxyuridine (BVdU) at any temp. and temp.-dependent resistance to acyclovir (ACV), buciclovir (BCV),

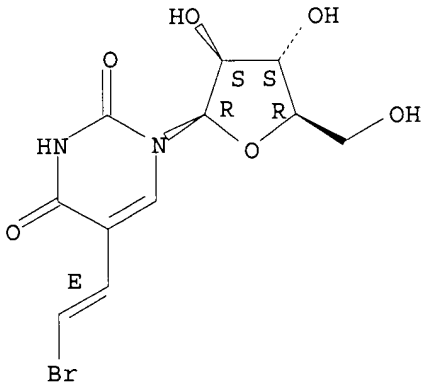
ganciclovir (DHPG), and fluoroiodoarabinouracil (FIAU). Above relatively low threshold levels of tk that varied depending on the drug tested, virsues exhibited full sensitivity to ACV, BCV, DHPG, and FIAU at 34.degree.. Below these threshold levels, however, decreases in drug sensitivity were linear with decreases in tk levels, forming the basis of a pharmacol. assay for tk gene expression. Studies of thymidine (TdR) anabolism in infected 143 tk- cells showed that when high TdR concns. were added to the medium, KG111 directed thymidine monophosphate (TMP) formation at rates consonant with the amt. of tk polypeptide produced by the mutant. When low concns. of TdR were added to the medium, however, KG111 directed TMP formation at a rate similar to that directed by wild-type virus, indicating that the truncation of the tk polypeptide had little or no effect on tk activity at 34.degree.. Subsequent anabolism to thymidine diphosphate and thymidine triphosphate was reduced in KG111-infected cells, indicating a defect in TMP kinase activity that explains this mutant's resistance to BVdU. Despite the low levels of tk and TMP kinase activity expressed by KG111, this mutant established reactivatable latent infections as efficiently as wild-type virus in a mouse model.

IT **77181-69-2**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(antiviral activity of and resistance to, herpes simplex virus thymidine-thymidylate kinase in relation to)

RN 77181-69-2 HCAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 33 OF 37 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1987:188499 HCAPLUS

DOCUMENT NUMBER: 106:188499

TITLE: Antiviral activity of various 1-.beta.-D-arabinofuranosyl-E-5-halogenovinyluracils and E-5-bromovinyl-2'-deoxyuridine against salmon herpes virus, Oncorhynchus masou virus (OMV)

AUTHOR(S): Suzuki, Satoru; Machida, Haruhiko; Saneyoshi, Mineo

CORPORATE SOURCE: Fac. Pharm. Sci., Hokkaido Univ., Sapporo, 060, Japan

SOURCE: Antiviral Research (1987), 7(2), 79-86
CODEN: ARSRDR; ISSN: 0166-3542

DOCUMENT TYPE: Journal

LANGUAGE: English

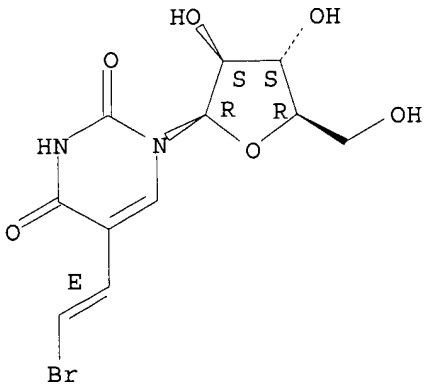
AB 1-.beta.-D-Arabinofuranosyl-E-5-bromovinyluracil (BVaraU) [77181-69-2], 1-.beta.-D-arabinofuranosyl-E-5-iodovinyluracil (IVaraU) [87535-95-3], 1-.beta.-D-arabinofuranosyl-E-5-chlorovinyluracil (CVaraU) [77181-70-5] and 1-.beta.-D-arabinofuranosyl-5-vinyluracil (VaraU) [74886-33-2] were examd. for antiviral activity against salmon herpes virus, Oncorhynchus masou virus (OMV) in vitro by using Yamame (O. masou) kidney cells. BVaraU, IVaraU, CVaraU and VaraU were highly active against OMV; 50% inhibitory concn. (IC50): 0.01, 0.003, 0.003 .mu.g/mL, resp. The IC50 of 5-bromovinyl-2'-deoxyuridine [82768-44-3] was 0.3 .mu.g/mL. The lower activity may be due to cleavage of it N-glycosyl linkage by pyrimidine nucleoside phosphorylase (i.e. thymidine phosphorylase [9030-23-3]) during the incubation period. The arabinofuranosyl counterparts are resistant to this (these) enzyme(s). Both OMV-induced DNA polymerase [9012-90-2] and cellular DNA polymerase .alpha. were markedly inhibited by BVaraU 5'-triphosphate [79551-90-9]. In an in vivo study, daily immersion of OMV-infected chum salmon (O. keta) fry into an aq. soln. of BVaraU (5 .mu.g/mL, 30 min/day, 30 times) did not increase the life span of infected fish.

IT **77181-69-2 77181-70-5 87535-95-3**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antiviral activity of, against salmon herpes virus)

RN 77181-69-2 HCAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

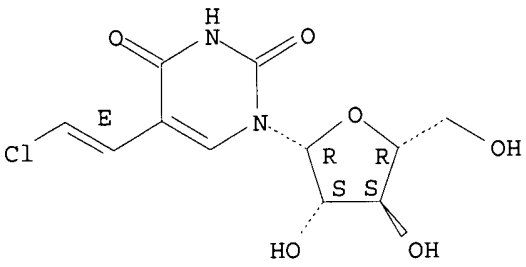
Absolute stereochemistry.
Double bond geometry as shown.



RN 77181-70-5 HCAPLUS

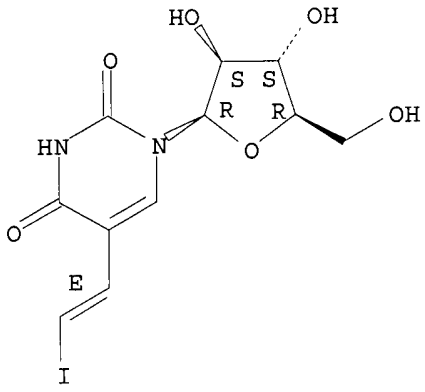
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-chloroethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 87535-95-3 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-iodoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 34 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:179778 HCAPLUS
DOCUMENT NUMBER: 104:179778
TITLE: Comparison of susceptibilities of varicella-zoster virus and herpes simplex viruses to nucleoside analogs
AUTHOR(S): Machida, Haruhiko
CORPORATE SOURCE: Res. Lab., Yamasa Shoyu Co. Ltd., Choshi, 288, Japan
SOURCE: Antimicrobial Agents and Chemotherapy (1986), 29(3), 524-6
CODEN: AMACCQ; ISSN: 0066-4804
DOCUMENT TYPE: Journal
LANGUAGE: English

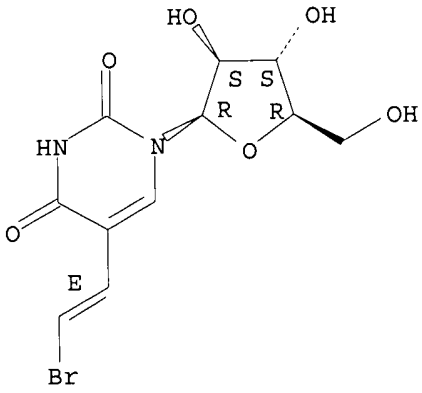
AB The susceptibilities of varicella-zoster virus (VZV) and herpes simplex virus type-1 (HSV-1) and type-2 (HSV-2) to 17 nucleoside analogs were compared by a plaque-redn. assay with human embryonic lung fibroblast cells. The susceptibility of VZV to certain nucleoside analogs was different from that of HSV-1. Against VZV, the 5-halovinyl-arabinosyluracils were the most potent of the compds. tested.

IT **77181-69-2 77181-70-5 87535-95-3**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antiviral activity of, against varicella zoster and herpes simplex)

RN 77181-69-2 HCAPLUS

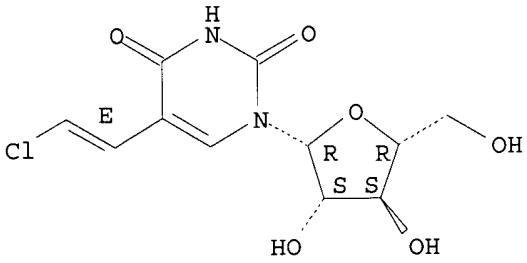
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



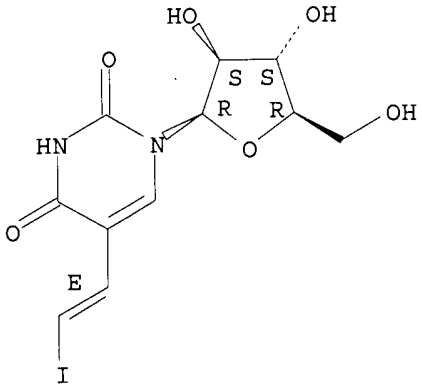
RN 77181-70-5 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-chloroethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

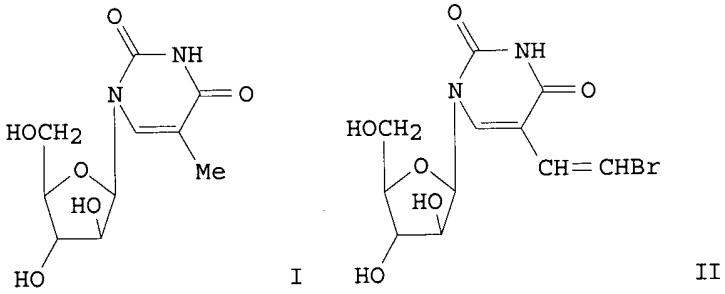


RN 87535-95-3 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-iodoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 35 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:17196 HCAPLUS
DOCUMENT NUMBER: 102:17196
TITLE: Investigation of antiviral activity of 1-.beta.-D-arabinofuranosylthymine (ara-T) and 1-.beta.-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil (BV-ara-U) in monkeys infected with simian varicella virus
AUTHOR(S): Soike, Kenneth F.; Baskin, Gary; Cantrell, Connie; Gerone, Peter
CORPORATE SOURCE: Delta Reg. Primate Res. Cent., Tulane Univ., Covington, LA, 70433, USA
SOURCE: Antiviral Research (1984), 4(5), 245-57
CODEN: ARSRDR; ISSN: 0166-3542
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB 1-.beta.-D-Arabinofuranosylthymine (ara-T)(I) [605-23-2] and 1-.beta.-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil (BV-ara-U)(II) [77181-69-2] were shown to antiviral activity in vitro and in vivo against simian varicella virus. Both compds. successfully prevented clin. disease caused by inoculation of African green monkeys with simian varicella virus, eliminating the development of rash and substantially suppressing viremia. Ara-T treatment was effective by either i.p. or oral routes of administration and BV-ara-U was active by both oral and i.m. routes. Ara-T, however, was assocd. with the appearance of marked signs of neurotoxicity. Histol. examn. of brain tissue demonstrated chromatolysis

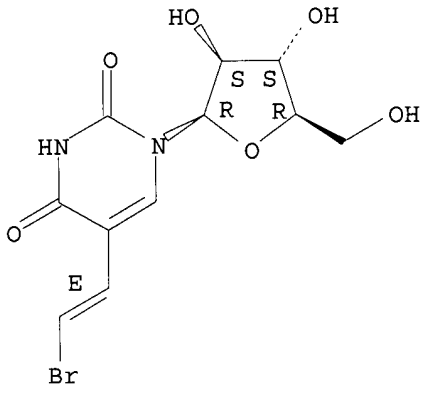
and pyknosis of neurons and pyknotic nuclei in glial cells. The neurol. impairment persisted in affected monkeys. This observation of central nervous system toxicity in monkeys is in contrast to studies in mice and rats where high doses of ara-T by multiple routes of administration were nontoxic. No apparent toxicity was obsd. in monkeys treated with BV-ara-U.

IT **77181-69-2**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antiviral activity of)

RN 77181-69-2 HCAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L43 ANSWER 36 OF 37 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1982:62635 HCAPLUS

DOCUMENT NUMBER: 96:62635

TITLE: Antiherpes activity of [E]-5-(1-propenyl)-2'-deoxyuridine and 5-(1-propenyl)-1-.beta.-D-arabinofuranosyluracil

AUTHOR(S): Stening, G.; Gotthammar, B.; Larsson, A.; Alenius, S.; Johansson, N. G.; Oberg, B.

CORPORATE SOURCE: Dep. Antiviral Chemotherapy, ASTRA Lakemedel AB, Sodertalje, Swed.

SOURCE: Antiviral Research (1981), 1(4), 213-23
CODEN: ARSRDR; ISSN: 0166-3542

DOCUMENT TYPE: Journal

LANGUAGE: English

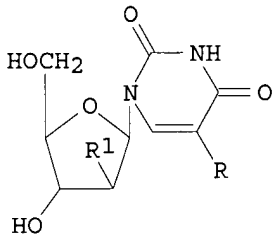
AB 5-(1-propenyl)-1-.beta.-D-arabinofuranosyluracil [74886-35-4] Was synthesized, and this compd. and (E)-5-(1-propenyl)-2'-deoxyuridine [66270-29-9]ere tested for inhibition of herpes virus multiplication. Only (E)-5-(1-propenyl)-2'-deoxyuridine was an active inhibitor reducing by 50% the plaque formation of herpes simplex virus type 1 (HSV-1) at .apprx.1 .mu.M. Comparison to the bromovinyl derivs. showed the following order of decreasing activity; (E)-5-(2-bromovinyl)-2'-deoxyuridine [69304-47-8] > 5-(2-bromovinyl)-1-.beta.-D-arabinofuranosyluracil [80434-16-8] .gtoreq. (E)-5-(1-propenyl)-2'-deoxyuridine > 5-(1-propenyl)-1-.beta.-arabinofuranosyluracil. HSV-1 mutants lacking thymidine kinase or resistant to acylcloguanosine were resistant to

(E)-5-(1-propenyl)-2'-deoxyuridine. All compds. seemed to be phosphorylated by HSV-1 thymidine kinase in a cell-free assay. The compds. were phosphorylated to a lower extent by cellular of HSV-2 thymidine kinase, and the HSV-2 strains tested were inhibited by <50% at 100 .mu.M in plaque assays. A selective inhibition of HSV-1 DNA synthesis by (E)-5-(1-propenyl)-2'-deoxyuridine was obsd. in infected cells indicating an effect on viral DNA polymerase. (E)-5-(1-Propenyl)-2'-deoxyuridine had a low cellular toxicity and a therapeutic effect when applied topically to HSV-1-infected guinea pig skin.

IT **80434-16-8**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(antiherpetic activity of)

RN 80434-16-8 HCAPLUS

L43 ANSWER 37 OF 37 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:62588 HCAPLUS
DOCUMENT NUMBER: 96:62588
TITLE: Selective antiherpes viral activity of 5-substituted derivatives of 1-.beta.-D-arabinofuranosyluracil
AUTHOR(S): Machida, Haruhiko; Sakata, Shinji; Shibuya, Susumu; Ikeda, Kazuyoshi; Nakayama, Chikao; Saneyoshi, Mineo
CORPORATE SOURCE: Res. Lab., Yamasa Shoyu Co. Ltd., Choshi, Japan
SOURCE: Antiviral Chemother.: Des. Inhib. Viral Funct., [Proc. Symp. Antiviral Chemother.] (1981), Meeting Date 1980, 207-17. Editor(s): Gauri, Kailash K. Academic: New York, N. Y.
CODEN: 46UVAL
DOCUMENT TYPE: Conference
LANGUAGE: English
GI



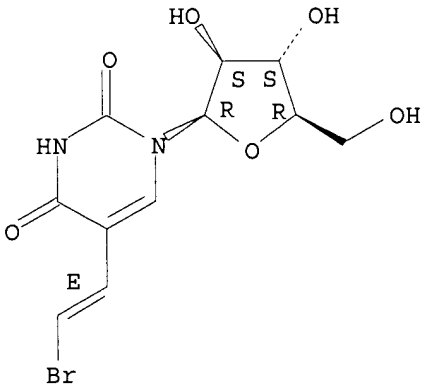
I

AB The antiviral (antiherpes) activities and cytotoxicities of a series of title compds. I (R = Et, CH:CHBr, CH:CHMe, etc.; R1 = H or OH) were studied. In general, the antiherpes activities of I (R = alkyl or alkenyl, R1 = OH) decreased with increasing chain length; these compds. had practically no growth inhibitory activity against various HEL-F cells. The antiherpes activities of the 5-acetonyl- [77181-59-0], 5-hydroxy- [5168-36-5], and 5-(methoxycarbonylmethyl)-2'-deoxyuridines [77181-57-8] were greater than those of their resp. arabinose derivs. The 5-vinylarabinouracil analogs showed a high margin of safety.

IT **77181-69-2 77181-70-5**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(antiherpes activity of, structure in relation to)

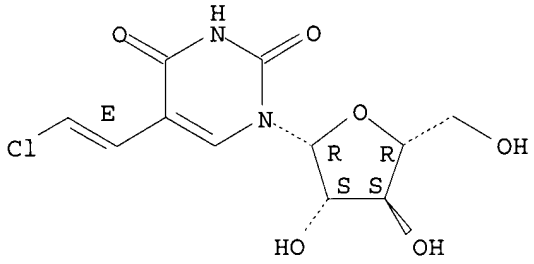
RN 77181-69-2 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-bromoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 77181-70-5 HCAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-.beta.-D-arabinofuranosyl-5-[(1E)-2-chloroethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



Richard,
Contact me if you need more answers for this structure. We can narrow the answer set using other methods if these answers don't have what you are looking for.

Searched by Thom Larson, STIC, 308-7309

Second compound listed on Search Request.

Point of Contact:
Thomas G. Larson, Ph.D.
703-308-7309
CM1, Rm. 6 B 01

```
=> file reg caplus
FILE 'REGISTRY' ENTERED AT 13:06:50 ON 02 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE 'CAPLUS' ENTERED AT 13:06:50 ON 02 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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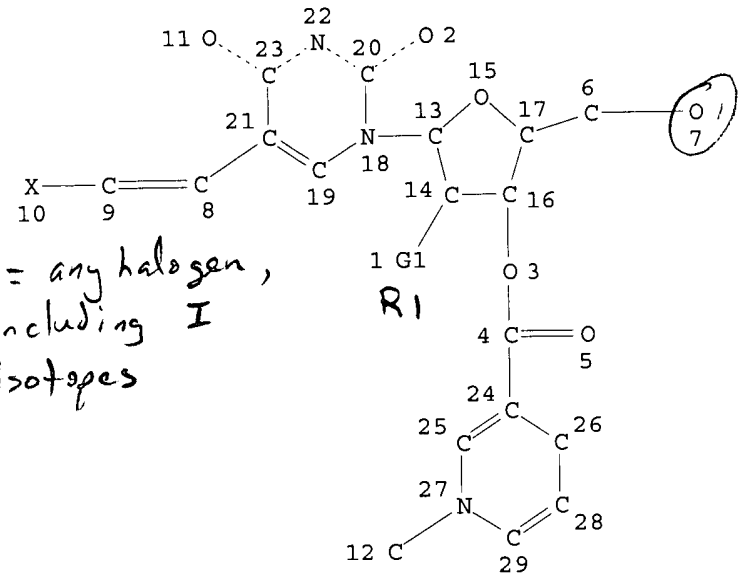
=> d que l28
L19                 STR
```



X = any halogen, including I isotopes

R1

R1: VAR G1=H/OH/F
NODE ATTRIBUTES:
CONNECT IS E1 RC AT (7) 1 non-H connection allowed @ 7 — limits O @ 7 to be an OH
CONNECT IS E3 RC AT 16
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 29

STEREO ATTRIBUTES: NONE

```
L20                 STR
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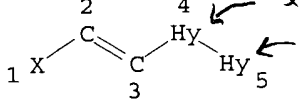


limited to 4C & 2N
limited to 4C & 1O

initial answer set (L22) obtain with this structure. L22 answer set then searched with structure above (L19).

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY UNS AT 4
GGCAT IS MCY SAT AT 5
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E4 C E2 N AT 4 (Hy)

E4 = exactly 4
E2 = exactly 2

Searched by Thom Larson, STIC, 308-7309

ECOUNT IS E4 C, E1 O AT 5 #y

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 5

STEREO ATTRIBUTES: NONE
L22 715 SEA FILE=REGISTRY SSS FUL L20 - Initial answer set using structure L20
L26 19 SEA FILE=REGISTRY SUB=L22 SSS FUL L19 - Search L22 answer set with structure L19
L28 6 SEA FILE=CAPLUS ABB=ON PLU=ON L26 - Search CAPLUS with answer set from Registry to get references disclosing hit structures.

=> D IBIB ABS HITSTR l28 1-6

L28 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:158289 CAPLUS
DOCUMENT NUMBER: 136:212894
TITLE: Production of labeled protein by foreign gene transferring for diagnosis, radiotherapy, chemotherapy, and gene therapy
INVENTOR(S): Knaus, Edward E.; Wiebe, Leonard I.; Morin, Kevin
PATENT ASSIGNEE(S): Can.
SOURCE: U.S. Pat. Appl. Publ., 27 pp., Cont.-in-part of U.S. Ser. No. 836,586, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002025296	A1	20020228	US 2001-855176	20010514
WO 9612508	A2	19960502	WO 1995-CA593	19951020

W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 1994-21223 A 19941021
WO 1995-CA593 W 19951020
US 1997-836586 B2 19970714

OTHER SOURCE(S): MARPAT 136:212894

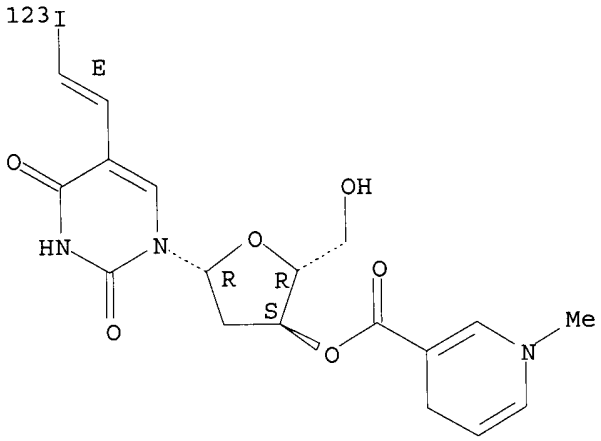
AB A method and use of a labeled compd. for monitoring the transfer of a foreign gene including selecting the foreign gene which has been isolated from a cell or virus and transferred into a cell population and selecting the labeled compd. which will interact selectively with a protein expressed by the foreign gene to produce a labeled product. The labeled compd. has a rate of expulsion from the cells which is greater than that of the labeled product. Further, the use and method include administering to the cells an ED of the labeled compd. such that the labeled compd. selectively interacts with the protein to produce the labeled product, waiting a period of time such that a substantial amt. of the labeled compd. has been expelled from the cells and such that a detectable amt. of the labeled product remains and detg. the extent and location of the protein by detecting the labeled product. The foreign gene is e.g. thymidine kinase gene derived from herpes simplex virus, human cytomegalovirus, varicella zoster virus and Epstein-Barr virus. The

labeled compd. prepd. were e.g. 123I-, 124I-, 125I-, or 131I-labeled analogs of (E)-5-(2-iodovinyl)-2'-fluor-2'-deoxyuridine (IVFRU).

IT **178179-41-4P 178179-42-5P 178179-43-6P**
178179-49-2P 178179-53-8P 178179-54-9P
178179-55-0P 178179-59-4P 178179-60-7P
178179-61-8P 401916-12-9P 401916-14-1P
401916-16-3P
RL: ANT (Analyte); BSU (Biological study, unclassified); DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prodn. of radiolabeled protein by foreign gene transferring for diagnosis, radiotherapy, chemotherapy, and gene therapy)

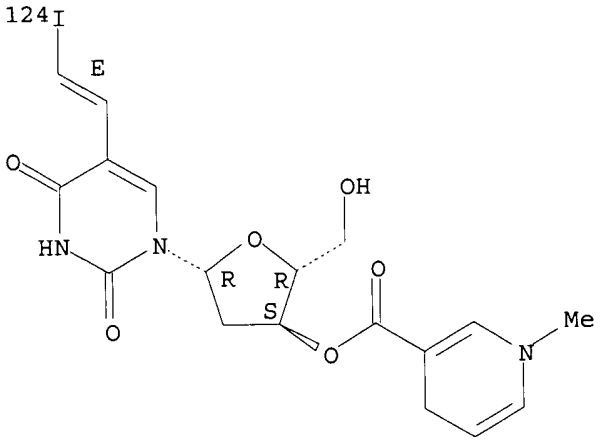
RN 178179-41-4 CAPLUS
CN Uridine, 2'-deoxy-5-[(1E)-2-(iodo-123I)ethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



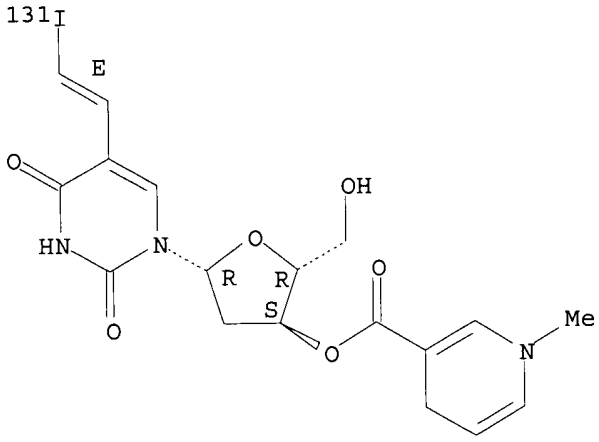
RN 178179-42-5 CAPLUS
CN Uridine, 2'-deoxy-5-[(1E)-2-(iodo-124I)ethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



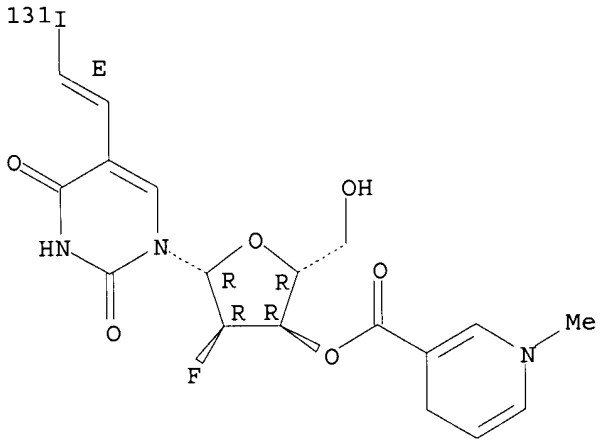
RN 178179-43-6 CAPLUS
CN Uridine, 2'-deoxy-5-[(1E)-2-(iodo-131I)ethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



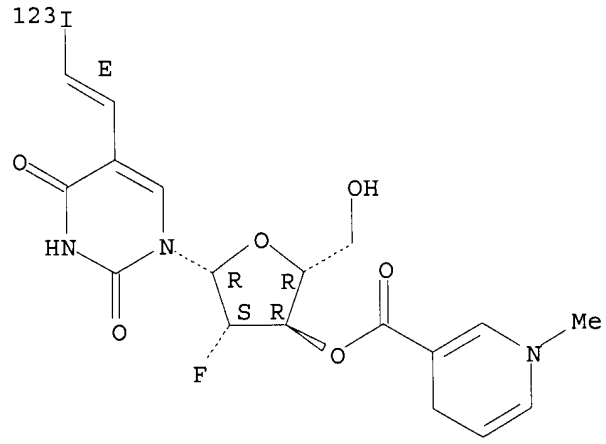
RN 178179-49-2 CAPLUS
CN Uridine, 2'-deoxy-2'-fluoro-5-[(1E)-2-(iodo-131I)ethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



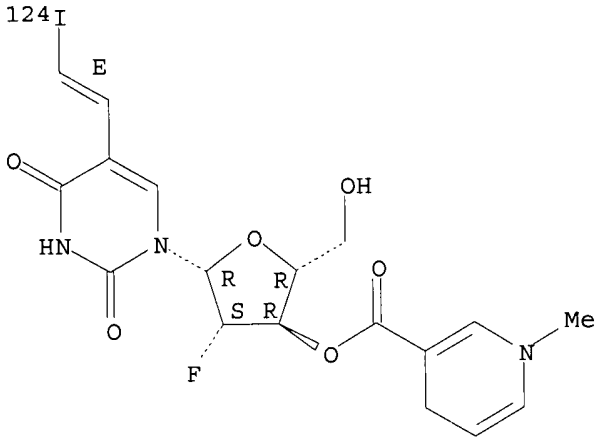
RN 178179-53-8 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[2-deoxy-3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-2-fluoro-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-123I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



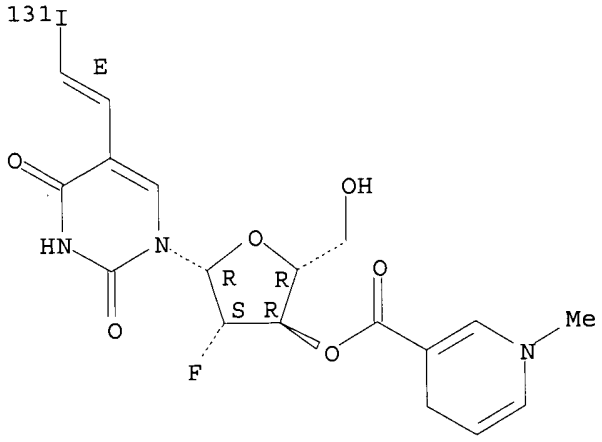
RN 178179-54-9 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[2-deoxy-3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-2-fluoro-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-124I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



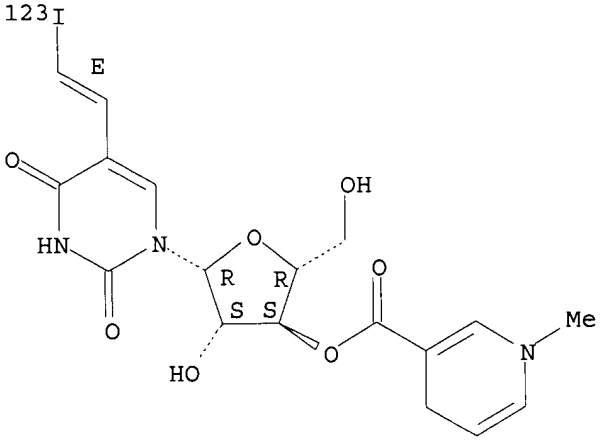
RN 178179-55-0 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[2-deoxy-3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-2-fluoro-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-131I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



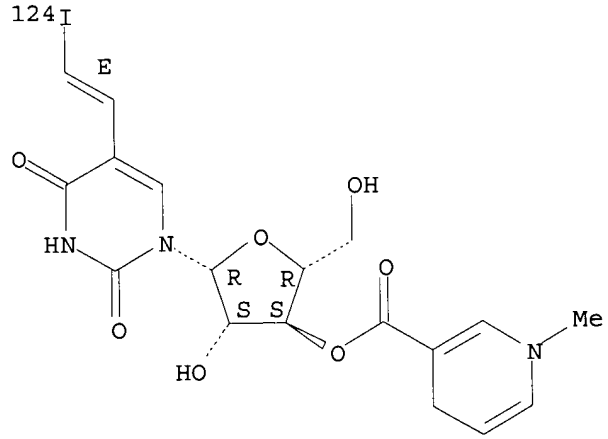
RN 178179-59-4 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-123I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



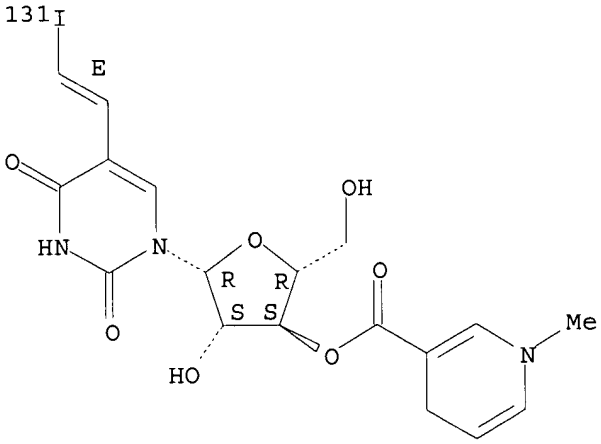
RN 178179-60-7 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-124I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



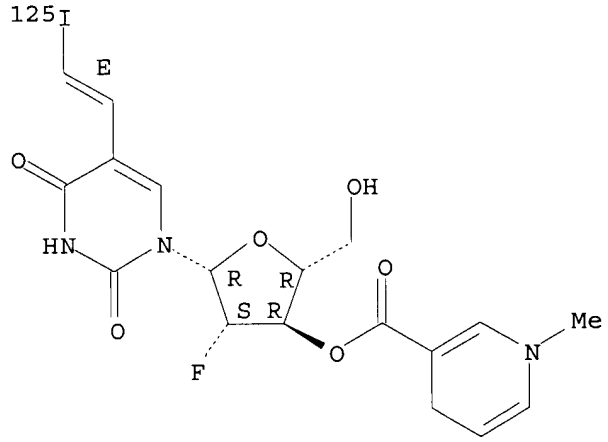
RN 178179-61-8 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-131I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



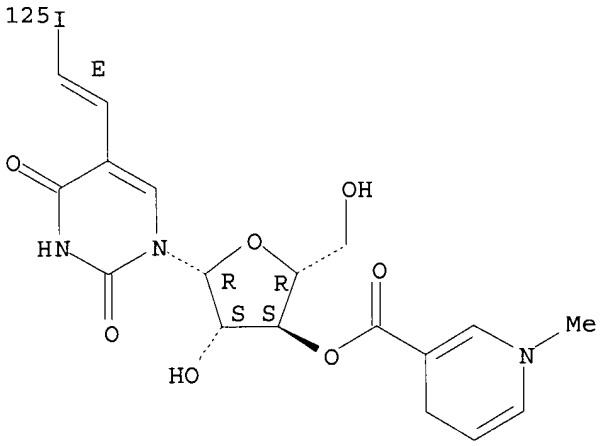
RN 401916-12-9 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[2-deoxy-3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-2-fluoro-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-125I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



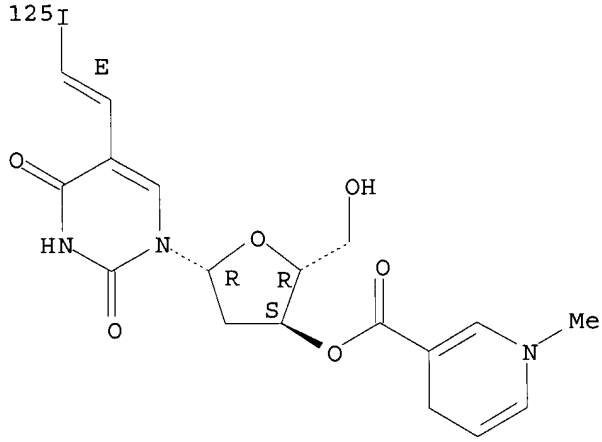
RN 401916-14-1 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-125I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



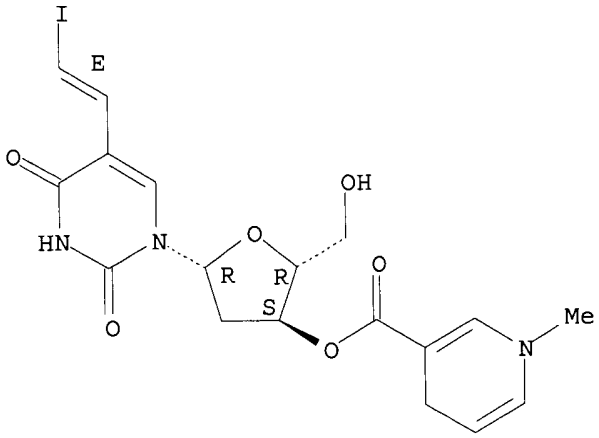
RN 401916-16-3 CAPLUS
CN Uridine, 2'-deoxy-5-[(1E)-2-(iodo-125I)ethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



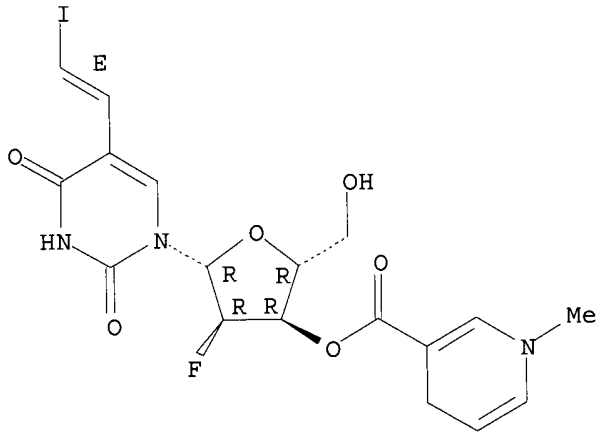
IT **135448-79-2DP**, radiolabeled **153085-34-8DP**, radiolabeled
166265-47-0DP, radiolabeled **178179-47-0P**
401915-39-7DP, radiolabeled
RL: ANT (Analyte); DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prodn. of radiolabeled protein by foreign gene transferring for diagnosis, radiotherapy, chemotherapy, and gene therapy)
RN 135448-79-2 CAPLUS
CN Uridine, 2'-deoxy-5-[(1E)-2-iodoethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



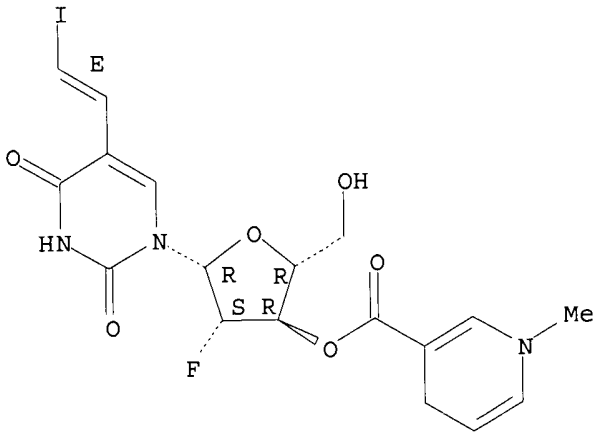
RN 153085-34-8 CAPLUS
CN Uridine, 2'-deoxy-2'-fluoro-5-[(1E)-2-iodoethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



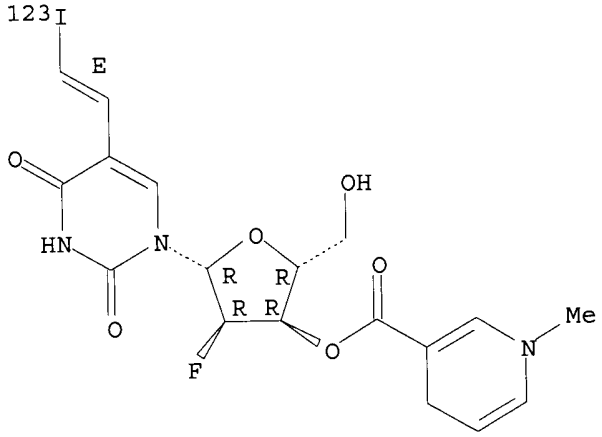
RN 166265-47-0 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[2-deoxy-3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-2-fluoro-.beta.-D-arabinofuranosyl]-5-[(1E)-2-iodoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



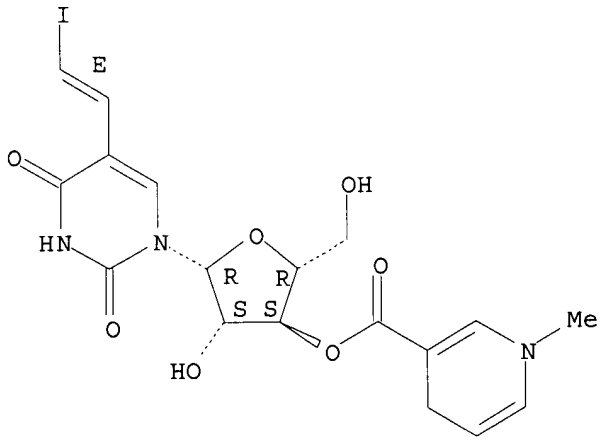
RN 178179-47-0 CAPLUS
CN Uridine, 2'-deoxy-2'-fluoro-5-[(1E)-2-(iodo-123I)ethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 401915-39-7 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-.beta.-D-arabinofuranosyl]-5-[(1E)-2-iodoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L28 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:45329 CAPLUS
DOCUMENT NUMBER: 137:190506
TITLE: Synthesis and biological investigations of 5-substituted pyrimidine nucleosides coupled to a dihydropyridine/pyridinium salt redox chemical delivery system
AUTHOR(S): Kumar, Rakesh; Wang, L.; Wiebe, L. I.; Knaus, E. E.
CORPORATE SOURCE: Department of Medical Microbiology and Immunology, Faculty of Medicine, University of Alberta, Edmonton, AB, T6G 2H7, Can.
SOURCE: Archiv der Pharmazie (Weinheim, Germany) (2001), 334(11), 351-356
CODEN: ARPMAS; ISSN: 0365-6233
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The syntheses, antiviral activities, and partition coeffs. (P) of 3'-O-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-coupled nucleosides are described. These novel compds. were designed in an effort to enhance the lipophilicity, and thereby the delivery to the CNS, without compromising the anti-HSV-1 activity of the parental nucleosides. We have previously reported the synthesis of 3'O-(1-methyl-1,4-dihydropyridyl-3-carbonyl) analogs of 5-iodo-, 5-vinyl-, and (E)-5-(2-iodovinyl)-2'-deoxyuridines (I, R = I, CH:CH2 OR (E)CH:CHI). We now report the synthesis of 5-iodo-3'-O-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-5'-O-acetyl-2'-deoxyuridine (II) and 3'-O-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2'-deoxyuridine (III). Quaternization of the 3'-O-(3-pyridylcarbonyl) compds. using iodomethane afforded the corresponding 1-methylpyridinium salts which were reduced with sodium dithionite to yield the corresponding 3'-O-1-methyl-1,4-dihydropyridyl-3-carbonyl compds. The deprotection of 3'-O-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-5-O-t-butyldimethylsilyl-2'-deoxyuridine with Bu4N+F- afforded III. I and II were evaluated for their

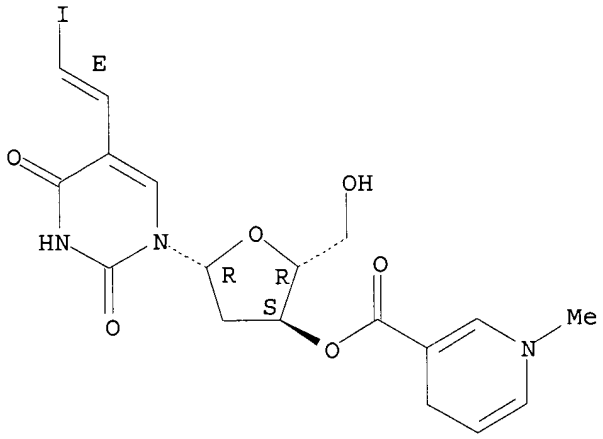
antiviral activity in vitro against HSV-1, HSV-2, HCMV, and VZV, and were found to retain anti-HSV-1, HSV-2 and VZV activity as compared to their parental nucleosides. In addn., the cellular toxicity of I and II was found to be lower than the parent nucleosides. The lipophilicity of I-III are enhanced substantially, compared to the parent nucleosides, as indicated by an increase in corresponding P values (1-octanol-water) upon replacement of the C-3' hydroxyl by 1-methyl-1,4-dihydropyridyl-3-carbonyl moiety.

IT **135448-79-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis and biol. investigations of 5-substituted pyrimidine nucleosides coupled to a dihydropyridine/pyridinium salt redox chem. delivery system)

RN 135448-79-2 CAPLUS

CN Uridine, 2'-deoxy-5-[(1E)-2-iodoethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:388479 CAPLUS
DOCUMENT NUMBER: 125:50744
TITLE: Synthesis and use of nucleoside analogs for monitoring gene transfection and for tissue imaging and therapy
INVENTOR(S): Knaus, Edward E.; Wiebe, Leonard I.; Morin, Kevin
PATENT ASSIGNEE(S): Governors of the University of Alberta, Can.
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9612508	A2	19960502	WO 1995-CA593	19951020

W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES,

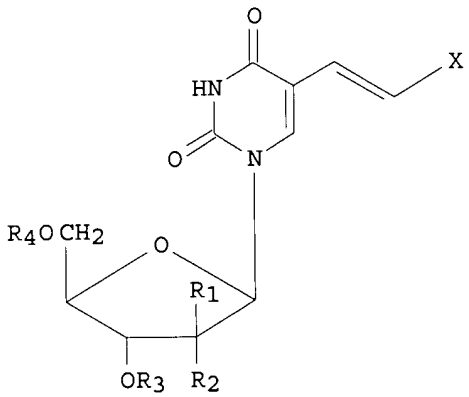
FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

CA 2202891	AA	19960502	CA 1995-2202891	19951020
AU 9536486	A1	19960515	AU 1995-36486	19951020
AU 715811	B2	20000210		
EP 784489	A2	19970723	EP 1995-934027	19951020
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
JP 10510046	T2	19980929	JP 1995-513558	19951020
US 2002025296	A1	20020228	US 2001-855176	20010514

PRIORITY APPLN. INFO.: GB 1994-21223 A 19941021
WO 1995-CA593 W 19951020
US 1997-836586 B2 19970714

OTHER SOURCE(S): CASREACT 125:50744; MARPAT 125:50744

GI



I

AB Diagnostic, radiotherapy, and chemotherapy methods which may be used in conjunction with gene therapy techniques, and the use of certain compds. in performing these methods are claimed. The methods are applicable to populations of cells into which a foreign gene has been transferred, which foreign gene expresses a protein which preferably is not naturally occurring within the cells. A compd. is selected which will interact selectively with the protein expressed by the foreign gene to produce a product which is trapped within the cells, is cytotoxic or cytostatic to the cells, or both, depending upon whether the compd. is being used for diagnostic purposes or for radiotherapy or chemotherapy purposes. The radiolabeled compd. is I (X=radioactive halogen; R=H, OH, F; R2=H, F; R3,R4=H, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl, 1-methyl-1,4-dihydropyridyl-3-carbonyl, 3-7C cycloalkylcarbonyl, alkylcarbonyl). In the case of diagnostic applications, trapping of the product, which is labeled, permits the product to accumulate in those of the cells in which the protein has been expressed by the foreign gene, thus facilitating detection of the labeled product in those cells. In the case of radiotherapy applications, trapping of the product, which is radioactive as a result of the compd. being radiolabeled, permits the product to accumulate in those of the cells in which the protein has been expressed by the foreign gene, thus facilitating radiotherapeutic effects directed specifically at those cells. In the case of chemotherapy applications, interaction of the protein with the compd. has either a

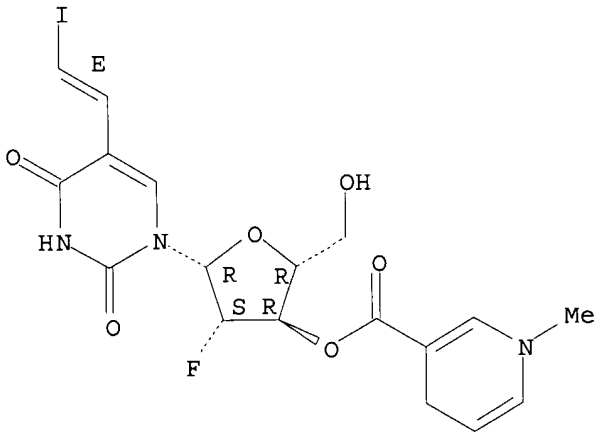
cytotoxic or a cytostatic effect on the cells, which is enhanced if the product is trapped within those of the cells or which the protein has been expressed. I (R1,R3,R4=H; R2=F; X=131I) was synthesized by reaction of 5-iodo-2'-fluoro-2'-deoxyuridine with (E)-1-(tri-n-butylstannyl)-2-(trimethylsilyl)ethane in the presence of bis(triphenylphosphine)Pd(II) chloride to produce the intermediate (E)-5-(2-trimethylsilylvinyl)-2'-fluoro-2'-deoxyuridine. The intermediate was reacted with [131I]NaI and N-chlorosuccinimide to prep. the radiolabeled compd. Tumor-bearing mice were developed from mice injected with herpes simplex virus 1 thymidine kinase-expressing KBALB cells. Following injection of the radiolabeled compd., the tumors were examd. by scintigraphic imaging. After treatment of the mice with ganciclovir, the size of the tumors was obsd. to decrease.

IT **166265-47-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and use of nucleoside analogs for monitoring gene transfection and for tissue imaging and therapy)

RN 166265-47-0 CAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 1-[2-deoxy-3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-2-fluoro-.beta.-D-arabinofuranosyl]-5-[(1E)-2-iodoethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



IT **178179-77-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and use of nucleoside analogs for monitoring gene transfection and for tissue imaging and therapy)

RN 178179-77-6 CAPLUS

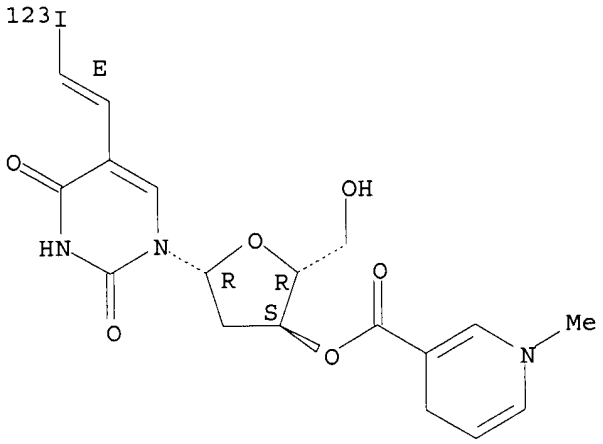
IT **178179-41-4P 178179-42-5P 178179-43-6P**
178179-47-0P 178179-48-1P 178179-49-2P
178179-53-8P 178179-54-9P 178179-55-0P
178179-59-4P 178179-60-7P 178179-61-8P
178179-71-0P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and use of nucleoside analogs for monitoring gene transfection and for tissue imaging and therapy)

RN 178179-41-4 CAPLUS

CN Uridine, 2'-deoxy-5-[(1E)-2-(iodo-123I)ethenyl]-, 3'-(1,4-dihydro-1-methyl-

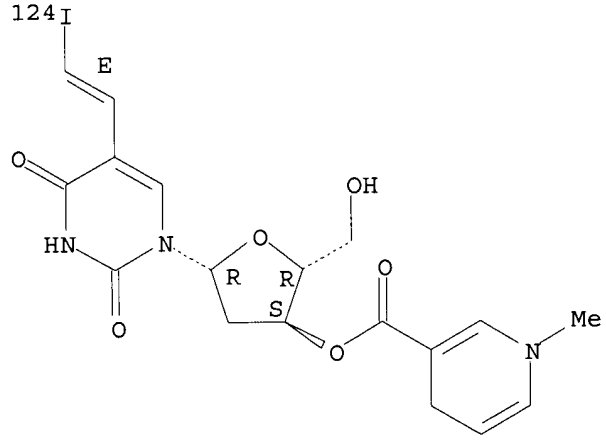
3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



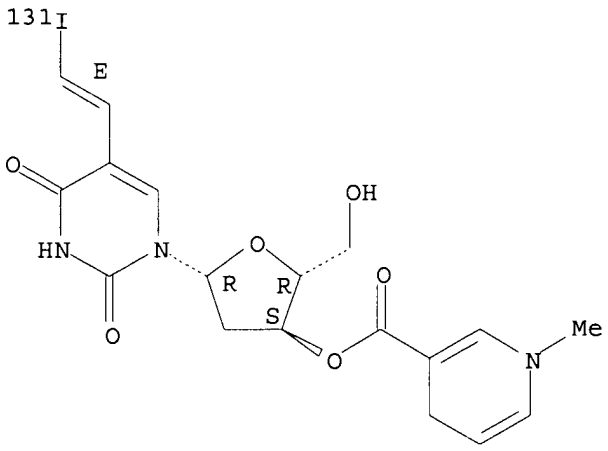
RN 178179-42-5 CAPLUS
CN Uridine, 2'-deoxy-5-[(1E)-2-(iodo-124I)ethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



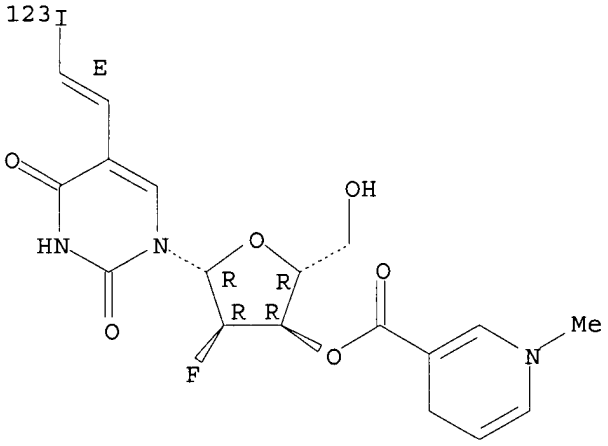
RN 178179-43-6 CAPLUS
CN Uridine, 2'-deoxy-5-[(1E)-2-(iodo-131I)ethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



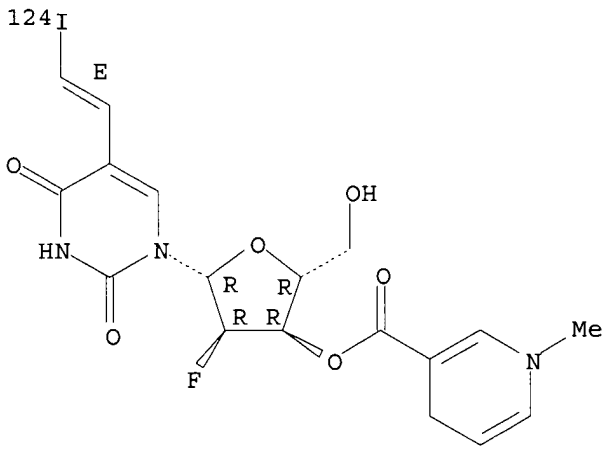
RN 178179-47-0 CAPLUS
CN Uridine, 2'-deoxy-2'-fluoro-5-[(1E)-2-(iodo-123I)ethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



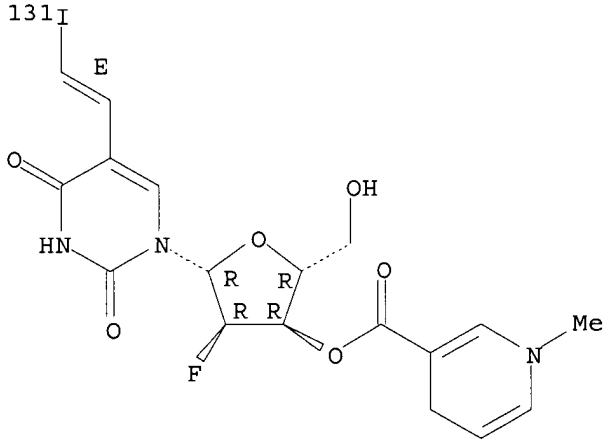
RN 178179-48-1 CAPLUS
CN Uridine, 2'-deoxy-2'-fluoro-5-[2-(iodo-124I)ethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate), (E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



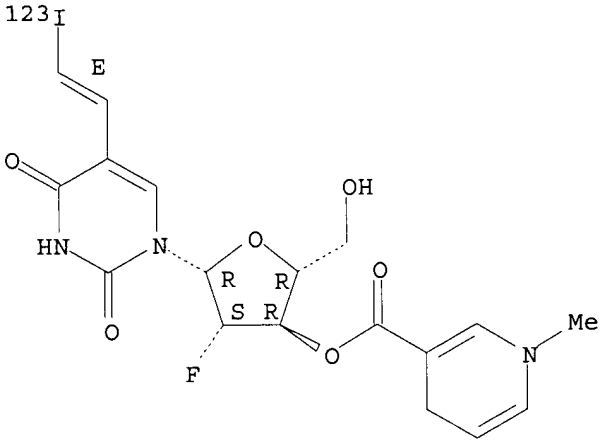
RN 178179-49-2 CAPLUS
CN Uridine, 2'-deoxy-2'-fluoro-5-[(1E)-2-(iodo-131I)ethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



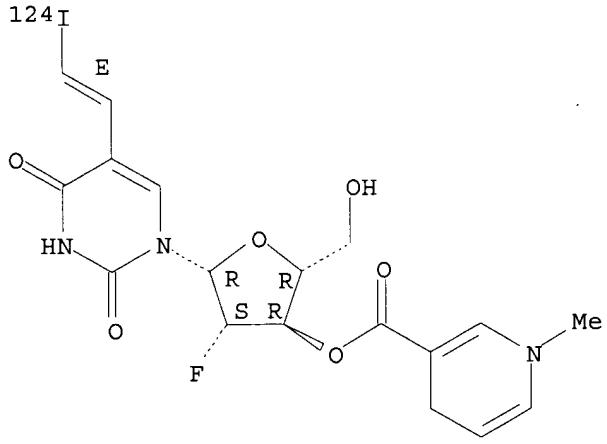
RN 178179-53-8 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[2-deoxy-3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-2-fluoro-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-123I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



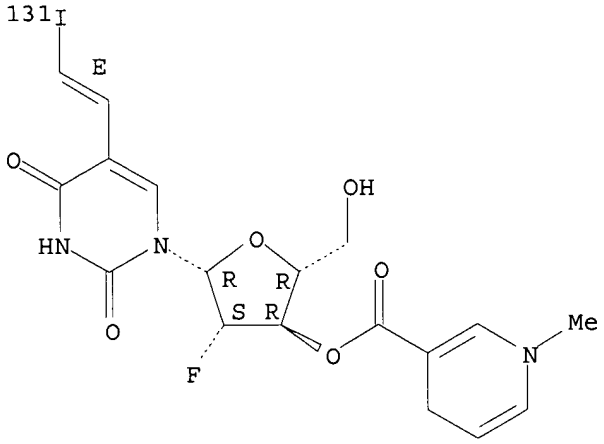
RN 178179-54-9 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[2-deoxy-3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-2-fluoro-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-124I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



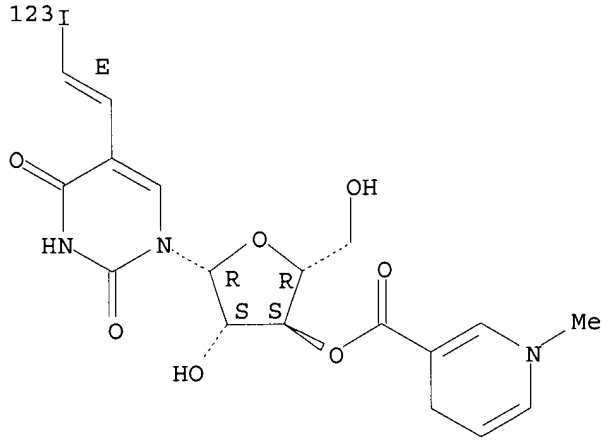
RN 178179-55-0 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[2-deoxy-3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-2-fluoro-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-131I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



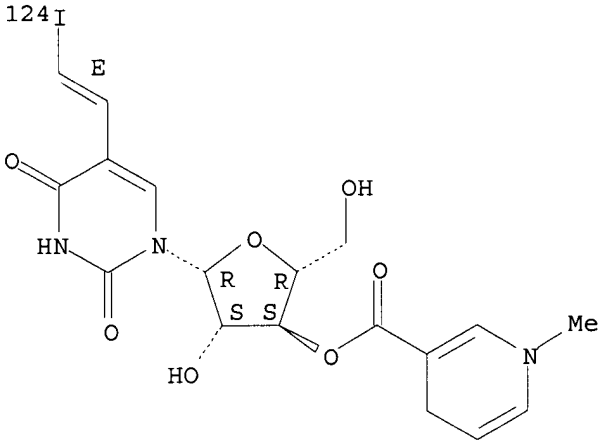
RN 178179-59-4 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-123I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



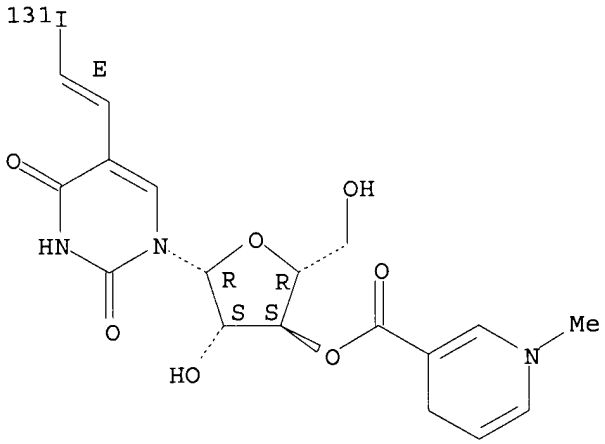
RN 178179-60-7 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-124I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 178179-61-8 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-.beta.-D-arabinofuranosyl]-5-[(1E)-2-(iodo-131I)ethenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 178179-71-0 CAPLUS

L28 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:679457 CAPLUS
DOCUMENT NUMBER: 123:102214
TITLE: Novel (E)-5-(2-iodovinyl)-2'-deoxyuridine derivatives as potential cytostatic agents against herpes simplex virus thymidine kinase gene transfected tumors
AUTHOR(S): Balzarini, J.; Morin, K. W.; Knaus, E. E.; Wiebe, L. I.; De Clercq, E.
CORPORATE SOURCE: Rega Institute Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Gene Therapy (1995), 2(5), 317-22
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Macmillan Scientific & Medical Division

Searched by Thom Larson, STIC, 308-7309

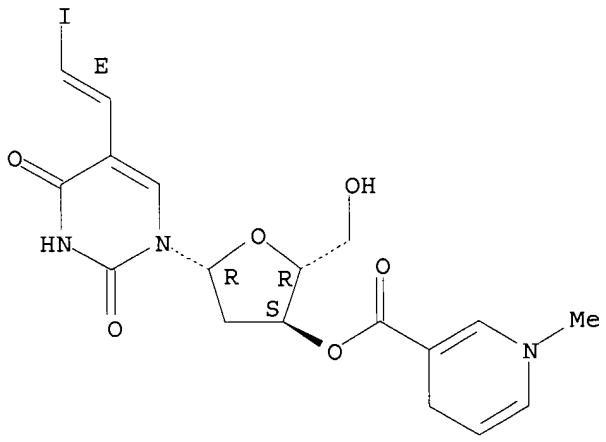
DOCUMENT TYPE: Journal
LANGUAGE: English

AB (E)-5-(2-Iodovinyl)-2'-deoxyuridine (IVDU), its 2'-fluoro-substituted derivs. IVFRU (with fluorine in the ribo configuration), IVFAU (with fluorine in the ara configuration), and the corresponding 3'-chem. delivery system (CDS), or 3'-O-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-substituted derivs. (IVDU-CDS, IVFRU-CDS and IVFAU-CDS) were evaluated for their cytostatic activity against wild-type (FM3A/0), thymidine kinase (TK)-deficient (FM3A/TK-), and herpes simplex virus type 1 (HSV-1) or HSV-2 thymidine kinase (tk) gene-transfected murine mammary carcinoma FM3A cells (FM3A TK-/HSV-1 TK+ and FM3A TK-/HSV-2 TK+). The test compds. proved highly inhibitory to the proliferation of HSVtk gene-transfected FM3A cells. Their cytostatic activity was within the 0.002 and 0.80 .mu.M range, a compd. concn. that is 1000- to 10,000-fold lower than that required to inhibit proliferation of wild-type FM3A/0 cells. The target for the cytostatic activity of the test compds. is the cellular thymidylate synthase. In contrast to the parent IVDU compd., IVFRU and IVFAU and their CDS-substituted derivs. proved resistant to phosphorolytic cleavage by human and bacterial thymidine phosphorylase and should be considered as promising candidate compds. for further evaluation for combined gene/chemotherapy of HSVtk gene-transfected tumor cells in animal models.

IT **135448-79-2 153085-34-8 166265-47-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel (E)-5-(2-iodovinyl)-2'-deoxyuridine derivs. as potential cytostatic agents against herpes simplex virus thymidine kinase gene transfected tumors)

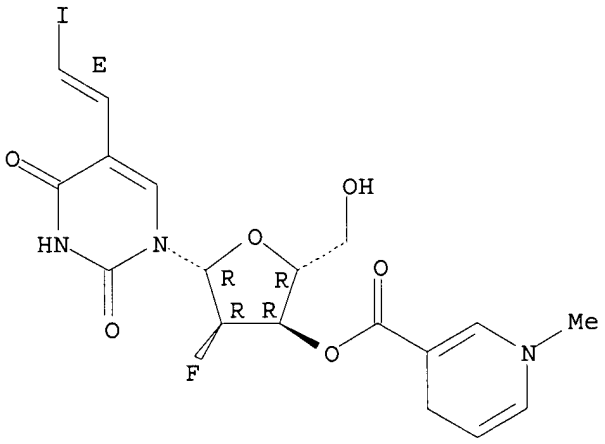
RN 135448-79-2 CAPLUS
CN Uridine, 2'-deoxy-5-[(1E)-2-iodoethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



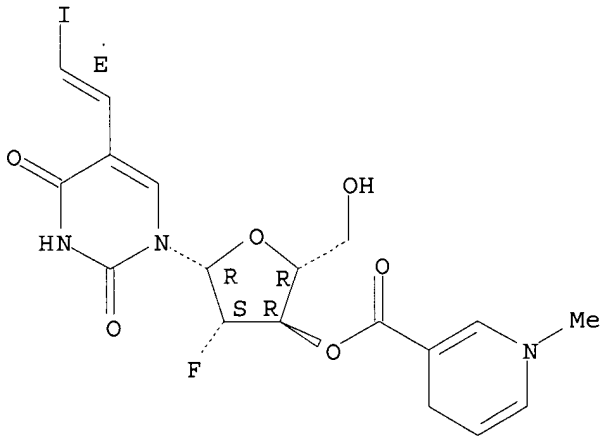
RN 153085-34-8 CAPLUS
CN Uridine, 2'-deoxy-2'-fluoro-5-[(1E)-2-iodoethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 166265-47-0 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 1-[2-deoxy-3-O-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-2-fluoro-.beta.-D-arabinofuranosyl]-5-[(1E)-2-iodoethenyl]- (9CI) (CA INDEX NAME)

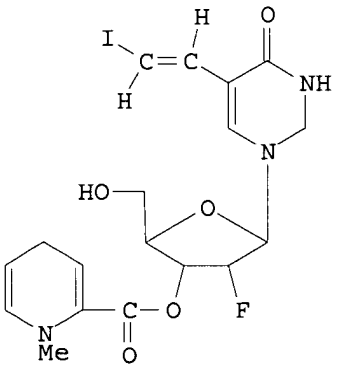
Absolute stereochemistry.
Double bond geometry as shown.



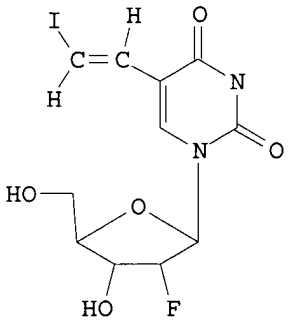
L28 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:135051 CAPLUS
DOCUMENT NUMBER: 120:135051
TITLE: Synthesis of (E)-5-(2-iodovinyl)-3'-O-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2'-fluoro-2'-deoxyuridine (IVFRU-CDS) for brain targetted delivery of IVFRU, an antiviral nucleoside
AUTHOR(S): Kumar, Rakesh; Knaus, Edward E.; Wiebe, Leonard I.
CORPORATE SOURCE: Fac. Pharm. Pharm. Sci., Univ. Alberta, Edmonton, AB, T6G 2N8, Can.
SOURCE: Nucleosides & Nucleotides (1993), 12(9), 895-904
CODEN: NUNUD5; ISSN: 0732-8311
DOCUMENT TYPE: Journal
LANGUAGE: English

Searched by Thom Larson, STIC, 308-7309

GI



I



II

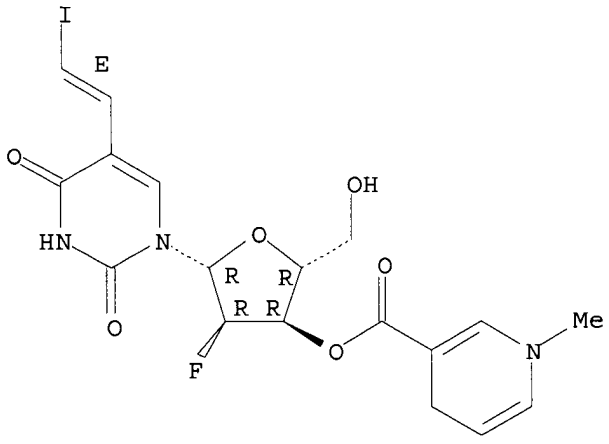
AB (E)-5-(2-Iodovinyl)-2'-fluoro-3'-O-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2'-deoxyuridine (I) was synthesized from 2'-fluoro-2'-deoxyuridine in 7% overall yield for future evaluation as a lipophilic, brain-selective, pyrimidine phosphorylase-resistant, antiviral agent for the treatment of Herpes simplex encephalitis (HSE).

IT **153085-34-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 153085-34-8 CAPLUS

CN Uridine, 2'-deoxy-2'-fluoro-5-[(1E)-2-iodoethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

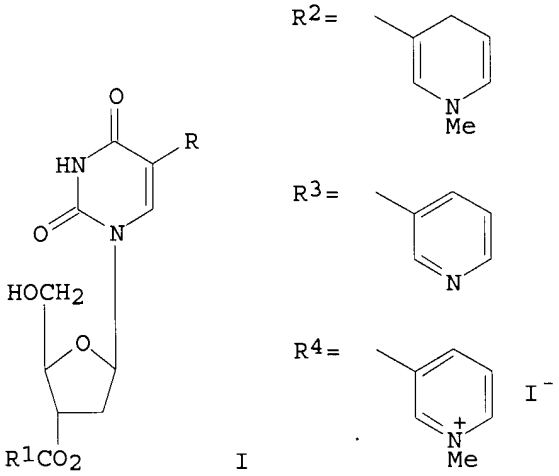
Absolute stereochemistry.
Double bond geometry as shown.



L28 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:492802 CAPLUS
DOCUMENT NUMBER: 115:92802
TITLE: Synthesis of brain-targeted 5-iodo-, 5-vinyl-, and (E)-5-(2-iodovinyl)-2'-deoxyuridine coupled to a dihydropyridine .dblharw. pyridinium salt redox chemical delivery system

Searched by Thom Larson, STIC, 308-7309

AUTHOR(S): Kumar, Rakesh; Ji, Gueijun; Wiebe, Leonard I.; Knaus, Edward E.
CORPORATE SOURCE: Fac. Pharm. Pharm. Sci., Univ. Alberta, Edmonton, AB, T6G 2N8, Can.
SOURCE: Journal of Heterocyclic Chemistry (1991), 28(3), 711-15
CODEN: JHTCAD; ISSN: 0022-152X
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 115:92802
GI



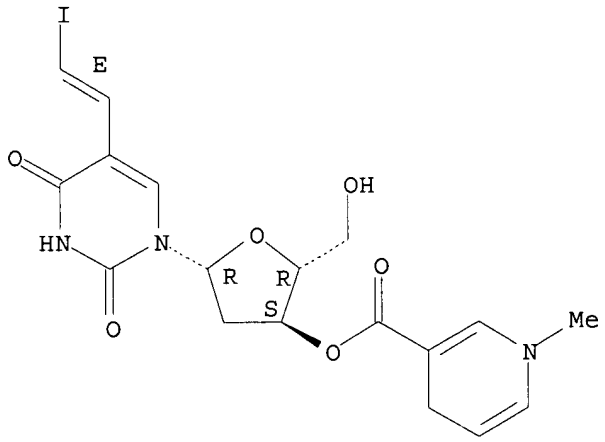
AB Iodo(dihydropyridylcarbonyl)deoxyuridines, e.g. I (R = iodo, CH:CH2, R1 = R2), were synthesized for future evaluation as lipophilic brain-selective antiviral agents for the treatment of herpes simplex encephalitis. Quaternization of I (R1 = R3) using MeI afforded the corresponding methylpyridiṅium salts I (R1 = R4) which was reduced with Na2S2O3 to yield the corresponding I (R1 = R2).

IT **135448-79-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as potential brain-selective antiviral agent)

RN 135448-79-2 CAPLUS

CN Uridine, 2'-deoxy-5-[(1E)-2-iodoethenyl]-, 3'-(1,4-dihydro-1-methyl-3-pyridinecarboxylate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.


I
E
O
HN
N
O
OH
O
R
R
S
O
O
N
Me